

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 02: Cancer

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA290201000006C

Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

December 2012

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 02: Cancer. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2012. <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>.

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the 43 topics for which (1) preliminary data from a trial intended to support regulatory approval for drugs (i.e., phase III data for most drugs and phase II data for accelerated approval drugs), phase II or III data for devices or procedures, or data from pilot programs were available; (2) information was compiled and sent for expert comment before September 21, 2012, in this priority area; *and* (3) we received six to nine sets of comments from experts between January 19, 2011, and October 19, 2012. (A total of 300 topics in this priority area were being tracked in the system as of October 26, 2012.) For purposes of this report, we aggregated related topics for summary and discussion (i.e., by drug class). Topics in this Executive Summary and report are organized alphabetically by disease state and by intervention within that disease state. We present 16 summaries on 20 topics (indicated by an asterisk) that emerged as having high-impact potential on the basis of expert comments and assessment of potential impact.

Priority Area 02: Cancer

Topics	High-Impact Potential
1. * Abiraterone (Zytiga) for treatment of metastatic castration-resistant prostate cancer	Moderately high
2. Autologous vascularized lymph node transfer for treatment of mastectomy-associated lymphedema	No high-impact potential at this time
3. Biophotonic system (LightTouch Scanner) for cervical cancer screening	No high-impact potential at this time
4. * Brentuximab vedotin (Adcetris) for recurrent or treatment-refractory anaplastic large cell lymphoma	Moderately high
5. * Brentuximab vedotin (Adcetris) for recurrent or treatment-refractory Hodgkin’s lymphoma	Moderately high
6. Carfilzomib (Kyprolis) for treatment of multiple myeloma	No high-impact potential at this time
7. Cologuard fecal DNA test for colorectal cancer screening	No high-impact potential at this time
8. * Concomitant colorectal cancer screening and annual influenza vaccine (FLU-FOBT) program	Lower end of the potential high-impact range
9. * Crizotinib (Xalkori) for treatment of advanced nonsmall cell lung cancer	Moderately high
10. * Digital 3-D breast tomosynthesis for breast cancer screening	High

Topics	High-Impact Potential
11. Electrical impedance scanner (SciBase III Electrical Impedance Spectrometer) for melanoma diagnosis	No high-impact potential at this time
12. * Enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer	Moderately high
13. * Everolimus (Afinitor) for treatment of advanced estrogen receptor-positive breast cancer	Moderately high
14. Everolimus (Afinitor) for treatment of pancreatic neuroendocrine tumors	No high-impact potential at this time
15. * Ipilimumab (Yervoy) for treatment of metastatic melanoma	Moderately high
16. Levonorgestrel-release intrauterine device for treatment of endometrial precancers and carcinoma	No high-impact potential at this time
17. Liver chemosaturation drug/device combination (melphalan/Chemosat) for treatment of melanoma metastases to the liver	No high-impact potential at this time
18. * MarginProbe System for intraoperatively identifying positive margins during breast cancer lumpectomy	Moderately high
19. MEK inhibitor (trametinib) for treatment of metastatic melanoma	No high-impact potential at this time
20. MelaFind multispectral dermoscope for detection of melanoma in suspicious skin lesions	No high-impact potential at this time
21. * Methylated Septin 9 blood test for colorectal cancer screening	Lower end of the potential high-impact range
22. Multikinase inhibitor (afatinib) for treatment of nonsmall cell lung cancer	No high-impact potential at this time
23. * Multikinase inhibitor (cabozantinib) for treatment of metastatic, medullary thyroid cancer	Lower end of the potential high-impact range
24. * Multikinase inhibitor (ponatinib) for treatment of chronic myelogenous leukemia and Philadelphia-chromosome-positive acute lymphoblastic leukemia	Lower end of the potential high-impact range
25. Mycobacterial cell wall–DNA complex (Urocidin) for treatment of nonmuscle-invasive bladder cancer	No high-impact potential at this time
26. Off-label metformin for treatment of breast cancer	No high-impact potential at this time
27. Off-label zoledronic acid (Zometa) for primary treatment of multiple myeloma	No high-impact potential at this time
28. Pazopanib (Votrient) for treatment of soft tissue sarcomas	No high-impact potential at this time
29. PCA3 assay as a triage test to inform biopsy decisionmaking for suspected prostate cancer	No high-impact potential at this time
30. * Pertuzumab (Perjeta) for treatment of advanced HER2-positive breast cancer	Moderately high
31. * Radium 223 (Alpharadin) for treatment of solid tumor bone metastases	Moderately high
32. Regorafenib (Stivarga) for treatment of colorectal cancer	No high-impact potential at this time
33. Regorafenib (Stivarga) for treatment of gastrointestinal stromal tumors	No high-impact potential at this time
34. * Ruxolitinib (Jakafi) for treatment of myelofibrosis	Lower end of the potential high-impact range
35. Sedasys computer-assisted sedation system for automated administration of propofol	No high-impact potential at this time
36. Sunitinib (Sutent) for treatment of pancreatic neuroendocrine tumors	No high-impact potential at this time
37. Therapeutic cancer vaccine (BiovaxID) for indolent follicular non-Hodgkin's lymphoma	No high-impact potential at this time
38. * Trastuzumab emtansine antibody-drug conjugate for treatment of advanced HER2-positive breast cancer	Moderately high
39. Tumor-treating fields therapy (NovoTTF-100A System) for brain cancer	No high-impact potential at this time

Topics	High-Impact Potential
40. * Vandetanib (Caprelsa) for treatment of metastatic, medullary thyroid cancer	Lower end of the potential high-impact range
41. * Vemurafenib (Zelboraf) for treatment of metastatic melanoma	High
42. * Vismodegib (Erivedge) for treatment of advanced basal cell carcinoma	Moderately high
43. Ziv-aflibercept (Zaltrap) for treatment of metastatic colorectal cancer	No high-impact potential at this time

Discussion

Topics that emerged as having potential for high impact in the cancer area included novel drugs and biologics for treatment, novel screening and diagnostic tests, a device used during surgical procedures, and a screening program. The conditions that these interventions addressed were solid tumors (advanced basal cell carcinomas, breast cancer, colorectal cancer, medullary thyroid cancer, melanoma, nonsmall cell lung cancer (NSCLC), prostate cancer, and solid tumor bone metastases) and hematologic malignancies (anaplastic large cell lymphoma [ALCL], chronic myelogenous leukemia [CML], Hodgkin's lymphoma [HL], myelofibrosis, and Philadelphia-chromosome-positive acute lymphoblastic leukemia [Ph+ ALL]).

The group of therapeutic agents includes both small-molecule and biologic drugs. Most small-molecule drugs have a well-defined mechanism of action and target a specific signaling pathway. Large-molecule drugs include antibody-drug conjugates (ADCs) directed to tumor-associated surface antigens and an immune stimulator. Diagnostic topics offered potentially simpler or purportedly improved solutions to existing technologies.

Breast Cancer

Digital 3-D Breast Tomosynthesis for Breast Cancer Screening

- Key Facts:** A limitation of two-dimensional (2-D) conventional mammography is that the radiologic images capture information from all tissue constituents along the path from the x-ray source to the detector. Therefore, breast features may be obscured by tissues that are in line with the x-ray path and above or below the feature of interest. Digital breast tomosynthesis (DBT) is an x-ray imaging modality that purports to overcome this potential limitation by imaging stabilized breast tissue in multiple angles for a given view by rotating the x-ray source in an arc around the target tissue. For example, rather than taking a single image in a given view as in conventional 2-D mammography, DBT involves taking 10–20 images with the angle of the x-ray beam shifted by approximately 1 degree in each image. Breast-tissue features that may obscure each other in images taken in one angle will be shifted relative to one another in other angles. By combining the information from each beam angle at the point where it crosses a given depth in the breast under examination, DBT can reconstruct images that represent serial slices through the breast. Developers propose that this imaging technology will improve mammographic imaging, potentially resulting in fewer recalls for inconclusive results, a reduced number of biopsies, and increased cancer detection. The first DBT system, the Selenia® Dimensions® 3D System (Hologic, Inc., Bedford, MA) received marketing approval from the U.S. Food and Drug Administration (FDA) in February 2011, based on results from two clinical trials of the system. This system is a software and hardware upgrade to the existing Selenia Dimensions 2D full-field digital mammography system.

According to data reported to ECRI Institute's MarketAnalytics Plus by health care facilities that have requested pricing, the average price quoted for a Selenia Dimensions 3-D system was \$480,110, which represents a \$221,000 increase over the average price quoted for the Selenia 2-D system. Prices quoted for the DBT upgrade option for the Selenia Dimensions system ranged from \$99,000 to \$180,000. The high upfront costs of capital equipment acquisition raise per-procedure costs for DBT relative to conventional 2-D digital mammography. Other factors that add to mammography screening costs with DBT include extra physician time to analyze multiple image sets, additional equipment-maintenance costs, and the need for more digital storage capacity and bandwidth to handle the data.

A survey of 11 representative, private, third-party payers that publish their policies online identified 8 payers that list coverage determinations for DBT. As of this writing, all these payers consider DBT to be experimental and/or investigational and exclude coverage for DBT-based screening or diagnosis. The current lack of reimbursement means that patients opting for DBT will typically incur an out-of-pocket fee, which has been reported to be in the range of \$50.

- **Key Expert Comments:** Experts commenting on this technology thought it has potential to bring incremental improvements in breast cancer screening by potentially improving breast cancer detection and reducing false-positive results. Such reductions, they noted, could obviate the need for unnecessary followup imaging and biopsy, which could save costs and reduce patient anxiety created by false-positive results. Experts thought that, given the likelihood that patients and clinicians would want to use this technology and considering the large changes in health care system costs and resources that using it would cause, DBT has potential for high impact.
- **Potential for High Impact:** High

Everolimus (Afinitor) for Treatment of Advanced Estrogen Receptor-Positive Breast Cancer

- **Key Facts:** Inhibitors of the mammalian target of rapamycin (mTOR) have been approved for treating various cancers such as renal cell carcinoma and pancreatic neuroendocrine tumors. Given their demonstrated efficacy in these cancers and the central role that the mTOR pathway plays in fundamental cellular processes related to tumorigenesis, researchers have undertaken a large number of clinical trials involving the use of mTOR inhibitors for treating a wide variety of cancers. Researchers recently reported results of a study of the mTOR inhibitor everolimus (Afinitor®, Novartis International AG, Basel, Switzerland) for treating estrogen receptor (ER)-positive breast cancer. This trial studied the drug in combination with the steroidal aromatase inhibitor exemestane in patients whose disease had progressed after treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole). In preliminary results from a 705-patient trial, researchers reported that adding everolimus to exemestane yielded a statistically significant improvement in progression-free survival of about 4 months. As a drug class, mTOR inhibitors are relatively well tolerated. The most common adverse events included stomatitis/mucositis, infections, rash, and fatigue; however, serious side effects have also been reported such as renal failure, elevated levels of blood glucose and lipids, and immunosuppression (which can lead to increased risk of infections). In July 2012, FDA approved everolimus for use in combination with exemestane to treat postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

- **Key Expert Comments:** Experts commenting on this intervention suggested that results for progression-free survival in endocrine-therapy-resistant metastatic breast cancer were promising for a condition with few treatment options. Experts hope to see data showing that the observed improvement in progression-free survival translates to improved overall survival, which they believe would have a large impact on patient care and treatment options.
- **Potential for High Impact:** Moderately high

MarginProbe System for Intraoperatively Identifying Positive Margins During Breast Cancer Lumpectomy

- **Key Facts:** Breast-conserving surgery followed by radiation therapy for early-stage breast cancer can achieve low recurrence rates equivalent to those achieved with total mastectomy. Achieving optimal outcomes with this technique, however, requires that the margins of the tissue excised during surgery be cancer free. If subsequent pathologic analysis reveals surgical margins are not cancer free, patients typically need to undergo a second surgical procedure to remove additional tissue. Therefore, techniques for identifying clean tissue margins during the initial surgical procedure are highly sought. Although several techniques have been developed (e.g., frozen sections, touch-prep cytology), the reported rate of secondary surgeries for unclear margins remains about 30%. The MarginProbe™ System (Dune Medical Devices, Ltd., Caesarea, Israel) purports to provide an objective means of rapidly assessing surgical margins intraoperatively using radiofrequency (RF) spectroscopy, which may be able to differentiate between normal tissue and cancerous tissue, based on bioelectric differences between the two tissue types. The MarginProbe algorithm is based on a training set of many comparisons between RF spectroscopy readings and pathology results and provides a binary (yes/no) answer as to whether the assessed margin is clean. In results from a 664-patient trial of the device, the MarginProbe System used in combination with standard intraoperative assessment was compared with standard intraoperative assessment alone. MarginProbe use reportedly increased the rates at which positive surgical margins were identified and additional tissue was removed to achieve clean surgical margins (72% for MarginProbe; 22% for standard assessment, $p < 0.0001$). This led to an approximate 50% reduction in the number of patients who needed to undergo a reexcision procedure. In November 2012, Dune Medical announced that it had received an Approvable Letter from FDA regarding the premarket approval application for the MarginProbe system. Final approval is contingent on finalization of the design of a post-approval study of the system.
- **Key Expert Comments:** Experts commenting thought this technology has potential to fill a significant unmet need for rapidly assessing surgical margins. Experts suggested that such a technology could significantly improve patient health outcomes by avoiding the need to perform secondary surgeries in a large number of women undergoing breast-conservation surgery. However, experts expressed a desire to see more data that definitively determined whether the system actually improved the rate of positive-margin detection and adequate excision of additional tissue for most patients.
- **Potential for High Impact:** Moderately high

Novel Targeted Therapies (Trastuzumab Emtansine; Pertuzumab [Perjeta]) for Advanced HER2-Positive Breast Cancer

- **Key Facts:** HER2-positive breast cancer is a subclass of invasive breast cancer characterized by expression of high levels of epidermal growth factor receptor family member HER2. This subtype comprises about 20% of breast cancer cases and is associated with more aggressive disease and poorer outcomes. Although treatment of HER2-positive breast cancer improved with the advent of HER2-targeted therapies such as trastuzumab (Herceptin®) and lapatinib (Tykerb®), many patients' cancers still progress with these treatments, and compounds with improved efficacy and/or efficacy against resistant disease are greatly needed.

One novel targeted therapy was recently approved, and another is in late-stage clinical trials for treating HER2-positive advanced breast cancer: trastuzumab emtansine and pertuzumab (Perjeta®, F. Hoffmann-La Roche, Ltd., Basel, Switzerland). Both are given as intravenous infusions. Trastuzumab emtansine (also being developed by Roche), formerly known as trastuzumab-DM1, is an ADC that couples an HER2-specific monoclonal antibody (trastuzumab) to a potent chemotherapeutic agent, the microtubule assembly inhibitor emtansine (DM1). They are coupled in such a way that emtansine is held in a stable inactive form outside the cell; only upon cellular uptake of the drug conjugate, mediated by binding of the antibody to the HER2 receptor, is emtansine released and activated. In this way, the cytotoxic activity of emtansine is targeted to cells expressing the HER2 receptor, potentially sparing many normal tissues from the drug's toxic effects. Trastuzumab emtansine is in many phase III trials for metastatic breast cancer. Roche recently announced that one of these trials (EMILA) testing trastuzumab emtansine against the standard second-line treatment of lapatinib and capecitabine had demonstrated increases in progression-free and overall survival as well as reducing the overall rate of severe adverse events. An FDA regulatory submission for this indication was made in the second half of 2012, and a decision on approval is scheduled for February 2013.

Pertuzumab is a novel HER2-specific monoclonal antibody that binds to a different site on the HER2 receptor than the available HER2-targeting monoclonal antibody trastuzumab. Mechanistically, pertuzumab is purported to prevent HER2 from interacting with other HER family receptors, which is required for their activation and function in breast cancer pathogenesis. Because pertuzumab functions through a mechanism of action distinct from that of trastuzumab, combining the use of these two HER2-specific antibodies has the potential to improve outcomes. Like trastuzumab-emtansine, pertuzumab is in several phase III trials for treating localized breast cancer after surgery and for treating metastatic breast cancer. The most advanced trial of pertuzumab studied the addition of pertuzumab to a standard first-line treatment for metastatic breast cancer (trastuzumab plus docetaxel). Preliminary results indicated that the addition of pertuzumab extended progression-free survival by about 6 months in this patient population. In June 2012, FDA approved pertuzumab for first-line treatment of HER-2 positive metastatic breast cancer in combination with trastuzumab and docetaxel. The reported wholesale cost per patient is about \$5,900 per month.

- **Key Expert Comments:** Overall, experts commenting on these interventions believe that trastuzumab emtansine and pertuzumab have significant potential to incrementally improve outcomes for patients with HER2-positive metastatic breast cancer. They thought that the shortcomings of the previous therapies represented a significant unmet need. Experts also thought that trastuzumab emtansine's potential to displace current standard of care for

HER2-positive metastatic breast cancer and the anticipated high cost of trastuzumab, emtansine, and pertuzumab could have significant impacts on managing disease in these patients.

- **Potential for High Impact:** Moderately high

Colorectal Cancer

Concomitant Colorectal Cancer Screening and Annual Influenza Vaccine (FLU-FOBT) Program

- **Key Facts:** Adherence to colorectal cancer (CRC) screening guidelines has been demonstrated to reduce CRC-related mortality, but only a minority of the population adheres to them, and about 50% of CRCs diagnosed in the United States are diagnosed at a late stage of disease. Therefore, innovations that have potential to improve CRC screening rates are highly sought. The FLU-FOBT (fecal occult blood test) program is an initiative that seeks to target the provision of CRC information and noninvasive FOBT kits to patients accessing the health care system to receive annual influenza vaccines. Influenza vaccination and CRC screening are in some ways natural partners because both are targeted to elderly patients and both are recommended to be performed annually. Pilot programs run by researchers at the University of California, San Francisco, in various care settings (e.g., hospital-based/managed-care based influenza vaccine clinics, pharmacy-based influenza vaccination campaigns, community health care clinics, primary care centers) demonstrated improved rates of FOBT completion and overall rates of CRC screening among patients who were part of FLU-FOBT-like programs compared with patients who received only an influenza vaccination. A study of 1-year followup from an initial program implementation found that a majority of clinics reported that they continued to offer FOBT with the influenza vaccine or as part of patient mailing kits.
- **Key Expert Comments:** Experts commenting on this intervention believe it is an interesting approach to increasing CRC screening rates that has significant potential to improve screening adherence in certain settings. However, experts questioned whether such a program could be implemented on a large scale, thereby limiting their view of its overall potential impact.
- **Potential for High Impact:** Lower end of the potential high-impact range

Methylated Septin 9 Blood Test for Colorectal Cancer Screening

- **Key Facts:** Research has demonstrated that cells undergo a range of epigenetic modifications (e.g., DNA methylation) during transformation to cancerous cells. In particular, elevated levels of certain methylated DNA species have been observed in the blood of patients with CRC, which could serve as a readily accessible marker for cancer screening. One such marker that has been shown to be present specifically in the blood of individuals with CRC is a methylated DNA derived from the Septin 9 gene, detection of which is being studied as a potential colon cancer screening test. Like other noninvasive colon cancer tests (e.g., FOBT), a positive result from the methylated Septin 9 test would require that the patient undergo a colonoscopy to confirm the result and biopsy and/or resect any suspect lesions. The methylated Septin 9 test is being developed by Epigenomics AG (Berlin, Germany), in collaboration with Abbott Laboratories (Abbott Park, IL). In 2011, Epigenomics reported data from a trial in which a subset of 7,940 patients undergoing

colonoscopy screening were also tested with the current version of the company's Septin 9 test (Epi proColon 2.0). The company reported that, compared with colonoscopy, the Septin 9 test had a sensitivity of 68% and a specificity of 80% for colorectal cancer. Data on the test's ability to detect precancerous, adenomatous polyps were not presented. Epigenomics has begun to submit data to FDA in support of a premarket approval application.

- **Key Expert Comments:** Overall, most experts commenting on this intervention thought that an accurate blood-based CRC screening test obtained through venipuncture (rather than testing a stool sample) could fundamentally change CRC screening practices by increasing the percentage of patients screened for CRC. However, regarding the Epi proColon 2.0 test specifically, experts were more cautious, questioning whether the reported sensitivity and specificity of the test were high enough and whether the high cost they anticipated for the test relative to other noninvasive options such as fecal occult blood testing would prevent its widespread adoption.
- **Potential for High Impact:** Lower end of the potential high-impact range

Hematologic Malignancies

Brentuximab Vedotin (Adcetris) for Recurrent or Treatment-Refractory Hodgkin's Lymphoma and Anaplastic Large Cell Lymphoma

- **Key Facts:** ADCs represent a class of cancer treatments in which highly toxic chemotherapy agents are coupled to monoclonal antibodies specific for molecules present on the surface of cancer cells. These targeted therapeutic agents are intended to deliver highly cytotoxic drugs to tumor cells while simultaneously reducing systemic side effects associated with untargated chemotherapy. CD30-positive malignancies such as HL and ALCL are rare, with only about 8,500 cases of HL and 2,250 cases of ALCL diagnosed annually in the United States. Although initial treatments for these conditions, in particular HL, are effective, patients with HL and ALCL often experience relapse, and in many cases the disease becomes resistant to available therapies. This has resulted in increased demand for new therapeutic options for recurrent/refractory disease. Brentuximab vedotin (Adcetris[®], Seattle Genetics, Inc., Bothell, WA, in collaboration with the Millennium Pharmaceuticals subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan) is an ADC that consists of a CD30-specific monoclonal antibody covalently attached to a potent, chemotherapeutic agent. It is intended to target CD30-expressing tumor cells and contains a novel linking system designed to allow it to remain stable in the bloodstream and release its cytotoxic drug only when internalized by cells. Common adverse effects reported in trials included nausea, fatigue, peripheral neuropathy, pyrexia, diarrhea, and neutropenia, which were characterized as "manageable." Rare but serious adverse events reported were progressive multifocal leukoencephalopathy, a potentially fatal brain infection. In August 2011, FDA approved brentuximab vedotin for HL that has failed to respond to an autologous stem cell transplantation or that has progressed after at least two multi-agent chemotherapy regimens in patients who are not autologous stem cell transplant candidates. FDA also approved the drug for treating ALCL after failure of at least one multi-agent chemotherapy. The initial drug pricing was set at about \$4,500 per vial; about three vials are used per treatment and 7–9 cycles of treatment given per patient, bringing the total cost for a regimen to a range of \$94,000–\$121,000. Brentuximab vedotin has significant potential to expand beyond the

FDA-approved indications, both in earlier lines of treatment for HL and ALCL and in other hematologic malignancies.

- **Key Expert Comments:** Overall, experts concurred that a significant unmet need exists for efficacious treatments for recurrent or treatment-refractory HL and ALCL. Given the lack of effective alternatives and the promising response rates reported in initial clinical trials, experts believe that wide adoption of brentuximab vedotin by physicians and patients is likely. However, the routine method of administration and the relatively small patient population that would be eligible for treatment with the drug would limit its overall impact on the health system.
- **Potential for High Impact:** Moderately high

Ruxolitinib (Jakafi) for Treatment of Myelofibrosis

- **Key Facts:** Myelofibrosis is a relatively rare myeloproliferative neoplasm characterized by bone marrow fibrosis, progressive anemia, and hematopoiesis that occurs outside the bone marrow and typically results in an enlarged spleen. Until FDA approval of ruxolitinib in November 2011, the agency had not approved any pharmacotherapy for treating myelofibrosis. Ruxolitinib is a small-molecule inhibitor of two tyrosine kinases (i.e., JAK1, JAK2) that function in the JAK/STAT pathway. Active JAK/STAT signaling promotes two important aspects of myelofibrosis disease pathogenesis: (1) clonal myeloproliferation (many cases of myelofibrosis harbor genetic mutations that lead to JAK/STAT pathway activation, in particular an activating mutation in JAK2) and (2) a proinflammatory state mediated by overexpression of cytokines. In two phase III clinical trials, treatment with ruxolitinib was reported to have led to significant improvements in spleen size and constitutional symptoms (e.g., fatigue); however, ruxolitinib treatment has not yet been shown to generate clear improvements in overall survival. Additionally, treating patients with ruxolitinib may actually exacerbate the anemia symptoms of myelofibrosis. Ruxolitinib was developed by Incyte Corp. (Wilmington, DE), which has reportedly priced the drug at \$7,000 per month. Most third-party payers list the drug as a specialty pharmaceutical requiring prior authorization for reimbursement.
- **Key Expert Comments:** Overall, experts believe that ruxolitinib addresses a significant unmet need for novel treatments for myelofibrosis and that the mechanism of action of ruxolitinib is highly suited to this indication. Although experts believe that it would likely be adopted by physicians and patients based on encouraging data regarding spleen size, experts were cautious, given the lack of data on patient survival and disease progression. Lastly, experts did not envision an oral medication intended for use in a relatively small patient population as having significant impacts on the health care system.
- **Potential for High Impact:** Lower end of the potential high-impact range

Multikinase Inhibitor (Ponatinib) for Treatment of Chronic Myelogenous Leukemia and Philadelphia-Chromosome-Positive Acute Lymphoblastic Leukemia

- **Key Facts:** CML typically is a slowly progressing disease that represents 20% of adult leukemias. Commonly diagnosed in middle age, CML progresses through chronic, accelerated, and blast phases characterized by increasing numbers of immature blood cells (i.e., myoblasts or blasts) in the blood and bone marrow. Unlike CML, ALL is more

commonly diagnosed in children younger than the age of 5 years; only about one in three ALL cases occurs in adults. Both CML and Ph+ ALL are characterized by the presence of the *BCR-ABL* oncogene, which generates a gene fusion product with constitutively active kinase activity that leads to the overproliferation of immature myoblasts. Tyrosine kinase inhibitors (TKIs) targeting oncogenic *BCR-ABL* are the current front-line therapies of choice for CML and Ph+ ALL. Although patients initially respond well to existing TKIs, such as dasatinib, imatinib, and nilotinib, many patients develop resistance to these *BCR-ABL* inhibitors. In particular, patients with CML who are harboring the T315I mutation in *BCR-ABL* are refractory to all current therapies targeting *BCR-ABL*. Ponatinib (ARIAD Pharmaceuticals, Inc., Cambridge, MA) is a novel TKI that inhibits TKI-resistant forms of *BCR-ABL*, including T315I as well as SRC, LYN, c-KIT, and members of the vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor families. Phase II trials have shown positive results for ponatinib monotherapy using surrogate endpoints in patients with disease resistant to existing TKIs. Ongoing phase II and III trials are investigating ponatinib use in the first-line treatment setting. ARIAD has submitted a new drug application (NDA) to FDA seeking accelerated approval of ponatinib for treating TKI-resistant or intolerant CML and Ph+ ALL. FDA has accepted the NDA and granted priority review status with a decision date of March 27, 2013. The existing data suggest that ponatinib may offer favorable response rates compared with the recently approved agent omacetaxine mepesuccinate (Synribo[®]), which is indicated for treating CML that is resistant to or intolerant of two or more TKIs.

- **Key Expert Comments:** Overall, experts were encouraged by results from phase II trials of ponatinib, citing a significant unmet need and potential health benefit for those with CML or Ph+ ALL that is resistant to existing TKIs. Clinical experts were particularly enthusiastic about the potential for ponatinib as a first-line treatment option, either as a monotherapy or in combination with other therapies. Although easy adoption and acceptance of this orally administered agent is predicted for both clinicians and patients, high costs remained a concern for experts, and several agreed that additional data are needed to determine ponatinib's long-term impact potential.
- **Potential for High Impact:** Lower end of the potential high-impact range

Lung Cancer

Crizotinib (Xalkori) for Treatment of Advanced Nonsmall Cell Lung Cancer

- **Key Facts:** Current chemotherapy options for patients with advanced NSCLC yield a relatively low response rate (25% to 30%) and 2-year survival rates of only 10% to 15%. Therefore, the need for new treatments is significant. In recent years, it has become clear that like other cancers, NSCLC is not a single disease, but rather a collection of related diseases with different molecular underpinnings. In particular, 2% to 7% of NSCLC tumors harbor genetic alterations that result in a fusion of the *ALK* gene with a second gene (often *EML4*). These gene fusions can produce a constitutively active ALK protein that can drive carcinogenesis. Experts see targeted inhibition of activated ALK as a promising therapeutic target for individuals with this ALK rearrangement. Crizotinib (Xalkori[®], Pfizer, Inc., New York, NY) is a small-molecule inhibitor of ALK kinase activity taken orally once daily. In August 2011, FDA granted the drug accelerated approval on the basis of two single-arm,

phase II clinical trials that exhibited a high rate of response to crizotinib therapy. More recently, in results from a phase III trial, crizotinib compared with standard second-line chemotherapies demonstrated improved progression-free survival in patients with *ALK*-mutation-positive NSCLC. Crizotinib is indicated for patients with locally advanced or metastatic NSCLC that is *ALK*-positive as detected by an FDA-approved companion diagnostic test, the Vysis *ALK* Break Apart FISH Probe Kit. The drug cost is about \$115,000 per patient per year (\$9,600 per month), and the list price of the companion diagnostic test is about \$225 per test. However, the full cost of the test also includes a fee for performing the test. Among 11 major, representative, third-party payers that publish their coverage policies, all list the drug as a specialty pharmaceutical and it typically requires prior authorization for reimbursement. The manufacturer has a payment-assistance program for select patients.

- **Key Expert Comments:** Experts commenting on this topic thought that the availability of an *ALK* inhibitor and its companion diagnostic test to identify appropriate patients for this treatment represents a significant advance in treatment options for this patient population. Additionally, experts suggested that the drug's availability would likely necessitate genetic profiling for most or all patients with NSCLC, potentially altering patient management and increasing costs associated with diagnosis and treatment. However, experts noted that the small percentage of patients with NSCLC who are *ALK*-mutation-positive would limit overall health impact for all patients with NSCLC.
- **Potential for High Impact:** Moderately high

Prostate Cancer

Novel Androgen-Targeting Therapies (abiraterone [Zytiga]; enzalutamide [Xtandi]) for Metastatic Castration-Resistant Prostate Cancer

- **Key Facts:** Until 2010, patients with a form of prostate cancer that had become resistant to first-line hormone therapy (castration-resistant prostate cancer [CRPC]) had only the chemotherapeutic agent docetaxel as an option that improved survival in some patients. The armamentarium for treatment grew in 2010 with FDA approval of the chemotherapeutic agent cabazitaxel (Jevtana[®]) and the therapeutic cancer vaccine sipuleucel-T (Provenge[®]). The latest additions to treatment options for metastatic, castration-resistant prostate cancer (mCRPC) came in April 2011 with approval of abiraterone (Zytiga[®], Johnson & Johnson, New Brunswick, NY) and in August 2012 with approval of enzalutamide (Xtandi[®], Medivation, Inc., San Francisco, CA). Abiraterone and enzalutamide are intended to improve on current methods of reducing androgen signaling, which is known to promote prostate cancer growth. These novel androgen-targeting compounds have expanded the use of androgen inhibitors to a later stage of prostate cancer that was previously thought to be independent of androgen signaling. Both abiraterone and enzalutamide were initially studied in patients with prostate cancer that had previously undergone treatment with docetaxel. Patients treated with either abiraterone or enzalutamide exhibited a 4- to 5-month increase in median overall survival compared with patients receiving placebo. Both drugs are also under study in patients who have not yet undergone treatment with docetaxel. Positive preliminary results for abiraterone have been reported from a phase III clinical trial in this patient population. Significant changes in the management of mCRPC will likely occur as

physicians incorporate abiraterone, cabazitaxel, enzalutamide, and sipuleucel-T into practice guidelines. The cost for 1 month of treatment with abiraterone or enzalutamide has been reported as about \$5,500 and \$7,450, respectively. Searches of 11 major, representative, private, third-party payers that publish their coverage policies online indicated that they generally reimburse abiraterone used for the FDA-approved indication and list the drug as a specialty pharmaceutical requiring prior authorization for reimbursement.

- **Key Expert Comments:** Overall, experts commenting on this intervention were quite positive regarding the potential of abiraterone and enzalutamide to improve both quality and quantity of life for patients with mCRPC. However, experts pointed out that the demonstrated improvement in survival duration is marginal (a few months) in patients whose disease has not responded to first-line chemotherapy and suggested that these drugs may have a larger impact when used earlier in treatment. Experts suggested that significant study of the proper sequential and/or combined use of abiraterone, enzalutamide, and other recently approved drugs for prostate cancer were needed.
- **Potential for High Impact:** Moderately high

Radium 223 (Alpharadin) for Treatment of Solid Tumor Bone Metastases

- **Key Facts:** Many solid tumors, in particular breast, prostate, and lung cancer, metastasize to bone, causing chronic pain and skeletal-related events (e.g., fractures) that adversely affect both patient quality of life and survival. Among the treatment options for bone metastases are radioactive molecules that have a natural affinity for sites of bone remodeling, which occurs at bone metastases. Preferential accumulation of the radioactive compound purportedly functions to concentrate the radiation dose at the target bone metastases. Although available radionuclides have shown efficacy in palliating bone pain, the type of radiation that they emit penetrates tissues deeply enough to negatively affect the bone marrow, which limits the deliverable dose and restricts their use to one of symptom palliation. Alpharadin[®] (a preparation of radium 223 developed by Algeta ASA, Oslo, Norway, and Bayer AG, Leverkusen, Germany) is a novel bone metastasis-targeting radiopharmaceutical that emits alpha particles, which have higher energies and more localized activity than radiation generated by available radiopharmaceuticals, potentially reducing the side-effect profile of treatment and more effectively targeting bone metastases. Recent results reported by the developers from a randomized, double-blind trial of 921 patients with CRPC with skeletal metastases who were ineligible for initial treatment or further treatment with docetaxel indicated increased overall survival of 3.6 months in patients treated with Alpharadin compared with patients treated with placebo. An independent committee recommended that the trial be stopped early because of the positive results. Investigators reported that, besides improving overall survival, treatment with Alpharadin improved secondary endpoints such as the time to first skeletal-related event, percentage of patients achieving normalized total alkaline phosphatase levels, and time to biochemical disease progression. Side effects were reported as being relatively benign, suggesting that it could potentially be used in combination with other prostate cancer treatments. Bayer recently initiated a phase III trial to collect additional long-term safety data, and an early-phase trial is examining Alpharadin in combination with the chemotherapeutic docetaxel for treating patients with CRPC with bone metastasis. Alpharadin is also the focus of a phase II study for treating breast cancer bone metastases.

- **Key Expert Comments:** Experts commenting on this topic thought that Alpharadin has significant potential to improve current treatments for bone metastases, particularly for patients with prostate cancer. Although experts thought Alpharadin would likely be widely adopted for this indication, the highly similar nature of Alpharadin to existing treatments suggested to experts that its adoption would have limited impact on health care system infrastructure and practices.
- **Potential for High Impact:** Moderately high

Skin Cancer

Ipilimumab (Yervoy) for Treatment of Metastatic Melanoma

- **Key Facts:** According to the American Academy of Dermatology, more than half of all new cases of melanoma are invasive at the time of diagnosis. Until recently, no clearly optimal treatments for metastatic melanoma were available. The monoclonal antibody ipilimumab (Yervoy[™], Bristol-Myers Squibb, New York, NY) is an immunotherapy that attempts to modulate an existing immune response to leverage that response. Ipilimumab has the potential to confront the problem of immune tolerance (i.e., lack of an immune response) to many cancers, in particular melanoma. The recent approvals of ipilimumab and the B-RAF inhibitor vemurafenib (Zelboraf[®]) represent the first therapies to show improved overall survival of about 4 months. FDA granted ipilimumab marketing approval in March 2011 for treating advanced melanoma. The drug's estimated per-patient cost is \$120,000 for a course of four infusions. More recently, data were published on ipilimumab as first-line therapy for metastatic melanoma in combination with the chemotherapeutic agent dacarbazine. Researchers reported a statistically significant improvement in overall survival of about 2 months for the ipilimumab group compared with the placebo group. Ipilimumab has a black box warning regarding the development of fatal immune-mediated adverse reactions due to T-cell activation and proliferation, which may involve any organ system. The most common side effects include dermatitis, endocrinopathy, enterocolitis, hepatitis, and neuropathy. Initial uptake of ipilimumab for treating patients with metastatic melanoma has been rapid and includes use as both a first- and second-line treatment.
- **Key Expert Comments:** Experts commenting on this intervention thought that clinical trials of ipilimumab demonstrated that the drug has a significant potential to meet an important unmet need for therapies that could improve overall survival in metastatic melanoma. However, this enthusiasm was tempered by the relatively small number of patients who achieved long-term benefit from the drug and the potential for serious adverse events. Despite these caveats, experts believe that ipilimumab would be widely adopted and that the high cost of the therapy would have a significant impact on the cost of care for this patient population.
- **Potential for High Impact:** Moderately high

Vemurafenib (Zelboraf) for Treatment of Metastatic Melanoma

- **Key Facts:** Vemurafenib (Zelboraf[®], Genentech unit of Roche) is a B-RAF inhibitor, and B-RAF inhibitors belong to a growing class of personalized cancer treatments. Use of these treatments is intended for patients whose tumors harbor specific genetic changes that are targeted by the therapies and, therefore, are likely to respond. Identifying the appropriate

patients for these therapies requires testing all patients with the cancer to identify the subset of patients for whom such personalized therapy may be appropriate. The drug target B-RAF plays a central role in the RAS/MAP kinase signal transduction pathway, which regulates cell growth and cell proliferation. Misregulation of this pathway has been demonstrated to be involved in multiple cancers. In particular, mutant versions of the *B-RAF* gene that encode a constitutively active B-RAF protein (e.g., B-RAF^{V600E}) have been identified in more than half of melanomas analyzed. Activated B-RAF is proposed to lead to hyperactivation of the downstream ERK/MEK/MAP kinase pathway, upon which melanomas may be dependent for growth and survival. Therefore, the specific inhibition of B-RAF kinase activity is a promising pharmacologic target. Researchers reported that vemurafenib increased overall survival and progression-free survival relative to treatment with dacarbazine in a phase III clinical trial. In August 2011, FDA approved vemurafenib for treating patients with unresectable or metastatic melanoma harboring a *B-RAF* mutation as detected by an FDA-approved companion diagnostic test, the cobas 4800 *B-RAF* V600 Mutation Test. The cost of vemurafenib is about \$9,400 per patient per month, and the company estimates a treatment course of about 6 months for a total of about \$56,400 per patient. Most third-party payers list the drug as a specialty pharmaceutical requiring prior authorization for reimbursement. Genentech has introduced a program, Zelboraf Access Solutions, to help some patients cover out-of-pocket costs. Positive phase III trial results were recently reported for a second B-RAF inhibitor, dabrafenib (GlaxoSmithKline, Middlesex, UK). A new drug application submission for dabrafenib is awaiting a decision by FDA.

- **Key Expert Comments:** An orally administered, small-molecule inhibitor of B-RAF kinase activity was considered by experts to have potential for high impact. Experts commenting on this topic thought that B-RAF inhibitors could fundamentally change treatment paradigms for metastatic melanoma because they will split a single syndrome into *B-RAF* mutation-positive and mutation-negative disease. This will necessitate testing all patients to determine their *B-RAF* status. Experts opined that although the potential of B-RAF inhibitors is limited by the fact that the vast majority of patients will eventually develop resistance to the therapy, these inhibitors are expected to be a central focus of melanoma treatment and clinical study in coming years.
- **Potential for High Impact:** High

Vismodegib (Erivedge) for Treatment of Advanced Basal Cell Carcinoma

- **Key Facts:** Until the FDA approval of vismodegib (Erivedge[®], Genentech subsidiary of F. Roche), no systemic therapy was approved for basal cell carcinomas that are not suitable for surgery. Vismodegib is an orally available, small-molecule inhibitor of a signaling pathway known as the Hedgehog pathway, the aberrant regulation of which has been implicated in a number of cancers. In particular, elevated levels of Hedgehog pathway activity have been observed in the majority of basal cell carcinomas, and preclinical data suggested that inhibition of this pathway could have an antitumor effect. In results from a single-arm, phase II trial of vismodegib treatment of 104 patients with locally advanced or metastatic basal cell carcinoma, investigators reported that vismodegib produced a 43% response rate for locally advanced disease, a 30% response rate for metastatic disease, and mean progression-free survival of 9.5 months. The most common adverse events reported were muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite, and diarrhea.

Additionally, serious adverse events were observed in 26 patients, and 4 of those events (blocked bile flow from the liver, dehydration with loss of consciousness, pneumonia accompanied by cardiac failure, and pulmonary embolism) were considered vismodegib-related. FDA approved the drug in January 2012 for treating patients with inoperable basal cell carcinomas. Ongoing studies are also examining potential vismodegib indications for treating patients with operable basal cell carcinomas. Genentech announced that vismodegib's average wholesale cost is \$7,500 per month per patient, and the estimated treatment duration is 10 months. Third-party payers list the drug as a specialty pharmaceutical requiring prior authorization for reimbursement. Genentech established a program called Access Solutions to facilitate access, including for patients who cannot afford the drug because of large copayments or lack of prescription drug insurance.

- **Key Expert Comments:** Experts commenting on this topic thought that vismodegib has significant potential as a first-in-class agent for treating basal cell carcinoma. Experts cited the compelling response rates in reported data thus far and a patient population lacking a systemic treatment option as the main factors signaling the potential importance of this drug; however, they wanted to see longer-term data and survival data. Experts thought that vismodegib's potential impact on the health system as a whole would be mitigated by the relatively small number of patients who would be targeted by this therapy.
- **Potential for High Impact:** Moderately high

Thyroid Cancer

Multikinase Inhibitors (Vandetanib [Caprelsa]; Cabozantinib) for Treatment of Metastatic, Medullary Thyroid Cancer

- **Key Facts:** Medullary thyroid cancer is a rare form of thyroid cancer that is diagnosed in about 1,500 patients per year in the United States. Before 2011, no effective treatment option was available for advanced disease that was not amenable to surgical resection. In April 2011, FDA approved vandetanib (Caprelsa[®], AstraZeneca, London, UK) as the first and thus far only medication specifically indicated for treating medullary thyroid cancer. Vandetanib is a small-molecule kinase inhibitor with activity against multiple tyrosine kinases that control multiple cancer-related cellular processes. Among vandetanib's targets is the RET (rearranged during transfection) receptor tyrosine kinase, mutations in which have been linked with both sporadic and familial forms of medullary thyroid cancer. Researchers reported results from a 231-patient, randomized controlled trial indicating that progression-free survival was longer for patients receiving the drug than for patients in the placebo arm; however, no difference was observed between groups for overall survival. The prescribing information for vandetanib carries a black box warning regarding the risks of heart rhythm abnormalities (i.e., QT prolongation, torsades de pointes) and sudden death. Only prescribers and pharmacies certified through the manufacturer's Risk Evaluation and Mitigation Strategy program, a restricted distribution program, may prescribe and dispense vandetanib. Reported cost for a 30-day supply of 300 mg vandetanib, taken once daily, is about \$10,000. Third-party payers list the drug as a specialty pharmaceutical requiring prior authorization.

Studies of other tyrosine kinase inhibitors with anti-RET activity are also under way for treating medullary thyroid cancer, and results from a late-stage clinical trial of cabozantinib (Exelixis, Inc., South San Francisco, CA) were recently reported. The developer announced

that cabozantinib met its primary endpoint of improving progression-free survival compared with placebo. An NDA was completed in May 2012, and a decision by FDA was scheduled for the end of November 2012.

- **Key Expert Comments:** Experts commenting on these inhibitors thought that the availability of vandetanib and the potential availability of cabozantinib for treating metastatic, medullary thyroid cancer represented a significant improvement in available treatment options for this condition. However, experts believe that the small patient population eligible for this treatment and the routine nature of its administration would limit the drugs' overall impact.
- **Potential for High Impact:** Lower end of the potential high-impact range

Breast Cancer Interventions

Digital 3-D Breast Tomosynthesis for Breast Cancer Screening

Conventional mammography uses x-rays to capture two-dimensional (2-D) images of breast tissue.¹ A limitation of the imaging technique is that the x-ray images capture information from all tissue constituents along the path from the x-ray source to the detector.² Therefore, breast features may be obscured by tissues that are in line with the x-ray path and above or below the feature of interest.

Digital breast tomosynthesis (DBT) is a new x-ray imaging modality that purports to overcome this potential limitation by imaging stabilized breast tissue in multiple angles for a given view by rotating the x-ray source in an arc around the target tissue. For example, rather than taking a single image in the craniocaudal view as in conventional 2-D mammography, DBT involves taking 10–20 images in the craniocaudal view with the angle of the x-ray beam shifted by approximately 1 degree in each image.² Breast tissue features that may obscure each other in one angle will be shifted relative to one another in other angles. By combining the information from each beam angle at the point where it crosses a given depth in the breast under examination, DBT can reconstruct images that represent serial slices through the breast. Developers propose that this imaging technology will improve mammographic imaging, potentially resulting in the following:²

- Fewer recalls of women for followup because of inconclusive mammography results
- Fewer biopsies
- Increased cancer detection, including in women with dense breasts

The first DBT system to be approved by the U.S. Food and Drug Administration (FDA), the Selenia[®] Dimensions[®] 3D System manufactured by Hologic, Inc. (Bedford, MA), received marketing approval in February 2011 based on results from two clinical trials of the system. This system is a software and hardware upgrade to the existing Selenia Dimensions 2D full-field digital mammography system.^{3,4}

In the first trial, 312 cases (of which 48 were biopsy-confirmed breast cancer) were imaged using conventional 2-D mammography and three dimensional (3-D) digital tomosynthesis.⁵ Twelve radiologists who had received training in interpreting 3-D digital tomosynthesis images interpreted the cases based on the 2-D data alone and based on a combination of the 2-D data and the 3-D tomosynthesis data. The study measured the area under the receiver operating characteristic (ROC) curve and the recall rate of noncancer cases. Researchers reported that interpretation of 2-D plus 3-D tomosynthesis data showed an improved area under the curve relative to interpretation of 2-D data alone for all experts (average increase in area of 0.071 for the American College of Radiology's breast imaging reporting and data system [BI-RADS[®]] ROC analysis [$p=0.0004$] and 0.072 for the probability of malignancy ROC analysis [$p=0.0001$]).⁵ They also reported that interpretation of 2-D plus 3-D tomosynthesis data exhibited a reduction in the recall rate for noncancer cases relative to interpretation of 2-D data alone, with a reduction in the average recall rate from 51.5% to 12.9%.⁵

In the second study, 310 cases (of which 51 were biopsy-confirmed breast cancer) were imaged using conventional 2-D mammography and 3-D digital tomosynthesis.⁵ Fifteen radiologists who had received training in interpreting 3-D digital tomosynthesis images interpreted the cases based on the following: (1) 2-D data alone; (2) a combination of 2-D data and 3-D tomosynthesis data from only the mediolateral oblique (MLO) view; and (3) a combination of 2-D data and 3-D tomosynthesis data from both the MLO view and the craniocaudal views. The study measured the area under the ROC curve and the recall rate of noncancer cases. Researchers reported that interpretation of 2-D plus 3-D tomosynthesis data in both views exhibited significant improvement

in the area under the ROC curve compared with both 2-D data alone and 2-D data in combination with 3-D tomosynthesis MLO data.⁵ They reported that recall rates for noncancer cases were 48.8% for 2-D data alone, 32.7% for 2-D plus 3-D MLO data, and 30.1% for 2-D plus full 3-D tomosynthesis data.⁵

Besides Hologic, several other developers are working to bring DBT systems to market in the United States (e.g., General Electric Co., Siemens AG).⁶ However, these DBT systems appear to be a year or more from commercial availability in the United States.

Hologic has indicated that the list price of the digital tomosynthesis option for the Selenia Dimensions system is \$150,000.⁷ According to data reported to ECRI Institute's MarketAnalytics Plus by health care facilities that have requested pricing, the average price quoted for a Selenia Dimensions 3-D system was \$480,110,⁸ which represents an average \$221,000 increase over the average price quoted for the Selenia 2-D system.⁹ Prices quoted for the DBT upgrade option for the Selenia Dimensions system ranged from \$99,000 to \$180,000.⁸

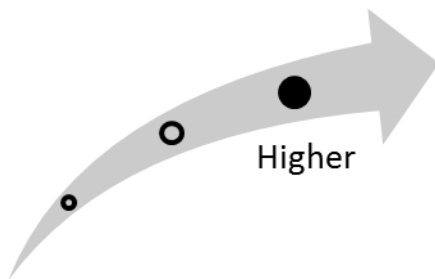
Due in part to the high upfront costs of capital equipment, the cost per procedure for DBT is higher relative to conventional 2-D mammography. Additional factors that contribute to an increased cost of mammography screening with breast tomosynthesis include extra physician time to analyze multiple image sets, additional equipment maintenance costs, and an increased need for digital storage and bandwidth to handle breast tomosynthesis data. A survey of 11 representative, private, third-party payers that publish their policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified 8 payers that list coverage determinations for DBT.¹⁰⁻¹⁷ All eight of these payers consider DBT to be experimental and/or investigational and therefore do not provide coverage for DBT-based screening or diagnosis. Because of the current lack of reimbursement for tomosynthesis, patients opting for digital breast tomosynthesis screening may be charged out of pocket for the service.¹⁸ Breast imaging centers have indicated that the out-of-pocket charge for adding digital breast tomosynthesis to standard 2D digital imaging is approximately \$50.^{19,20} Large prospective trials comparing DBT to full-field digital mammography are nearing the estimated completion date for their primary endpoints.^{21,22} Data reported from these trials and additional ongoing trials are likely to influence future coverage determinations.

Given these barriers to adoption, initial DBT uptake has initially been relatively slow. Hologic indicated that, in the first 18 months following approval, between 350 and 360 DBT units were placed in health care facilities, representing about 3% of mammography units present in Mammography Quality Standards Act and Program-certified facilities.^{23,24}

Clinical Pathway at Point of This Intervention

Primary breast cancer screening is typically performed using 2-D digital or film x-ray mammography.²⁵ After identification of an abnormality on screening mammography, patients typically undergo additional diagnostic imaging (e.g., diagnostic mammography, ultrasound, magnetic resonance imaging) and a physical examination. If these studies suggest the abnormality is cancerous, biopsy material may be obtained by fine-needle aspiration, core-needle biopsy, or open surgical biopsy.²⁵ The Selenia Dimensions 3D tomosynthesis system would be used in place of conventional 2-D x-ray mammography for breast cancer screening and followup diagnostic imaging of suspicious lesions.⁵

Figure 1. Overall high-impact potential: digital 3-D breast tomosynthesis for breast cancer screening



Overall, experts providing comments on this technology thought that it has potential to bring incremental improvements in breast cancer screening by potentially improving breast cancer detection and reducing false-positive results. Such reductions, they opined, could obviate the need for unnecessary followup imaging and biopsy, which could save costs and reduce patient anxiety created by false-positive results. Experts thought that, given the likelihood that patients and clinicians would want to use this technology and the large changes in health care system costs and resources that using it would cause, DBT has potential high impact. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Eight experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.²⁶⁻³³ The consensus among experts was that digital tomosynthesis has the potential to address two significant unmet needs in breast cancer screening: (1) finding cancers that conventional screening mammography misses, particularly in women with dense breasts, for whom conventional mammography has poor sensitivity; and (2) reducing the high rate of inconclusive or false-positive results seen with conventional mammography, which leads to many unnecessary recalls for followup imaging and biopsies.

Although experts agreed that DBT has the potential to improve sensitivity and specificity relative to conventional mammography, they were less certain about how large an impact digital tomosynthesis would have on these unmet needs. Multiple experts noted the incremental nature of the improvement in sensitivity and specificity. Additionally, one clinical expert questioned whether data from a retrospective study of a case series enriched with cancer cases should be generalized to the screening population, where breast cancer rates would be much lower. This expert suggested that digital tomosynthesis might initially be best used by being reserved for high-risk patients and/or patients with dense breast tissue. Lastly, one expert with a clinical background noted that although it has purported benefits, DBT could add to the problem of breast cancer over-diagnosis, in which slow-growing, noninvasive carcinomas that might not have affected patient health are detected and treated. But to the contrary, an expert with both a research and health systems perspective believes it has a high likelihood of becoming a replacement screening tool over time as hospitals upgrade their screening mammography technology, based on the assumption that it can potentially improve cancer detection, lower recall rates, and lower the proportion of biopsies that turn out to be negative because of a false-positive result from the prior screening. Ultimately, multiple experts suggested, ongoing, large clinical trials comparing DBT with 2-D digital images need to be completed before a clear case for switching to DBT in the screening setting could be justified.

Even if digital tomosynthesis provides only marginal improvements in sensitivity and specificity, experts thought, patients would be eager to receive screening with this technology, because it is the most advanced breast screening technology available. However, some experts

noted that patients may fear the increase in radiation dose incurred during DBT compared with conventional mammography.

Multiple experts noted that adoption of DBT as a screening tool would have significant impacts on health care facility infrastructure and staffing. They pointed out that facilities wishing to offer it would not only need to acquire the imaging system itself, but also increase digital bandwidth, data storage capacity, and the number of viewing workstations to accommodate the increased data generated by a tomosynthesis system. Furthermore, radiologists would need to be trained in the acquisition and interpretation of the data and the large amount of data generated would significantly increase the amount of time radiologists need to spend analyzing the data. Several experts suggested that the cost-benefit ratio of DBT may reduce the willingness of clinicians to adopt this technology. It may also affect payer decisions to reimburse the use of the technology.

Everolimus (Afinitor) for Treatment of Advanced Estrogen-Receptor-Positive Breast Cancer

The mammalian target of rapamycin (mTOR) plays a central role in a cell-signaling pathway regulating multiple cancer-related processes such as cell growth, proliferation, survival, and migration. Additionally, multiple mTOR-pathway molecules have been shown to be aberrantly expressed and/or mutated in various cancers, suggesting that mTOR inhibitors could function as anticancer agents. Based on this observation, a class of drugs that inhibit mTOR via a mechanism of action similar to that of the naturally occurring macrolide antibiotic rapamycin (also known as sirolimus) has been developed.³⁴ Rapamycin-like mTOR inhibitors have been approved for treating various cancers, including temsirolimus (Torisel[®]) for treating renal cell carcinoma³⁵ and everolimus (Afinitor[®], Novartis International AG, Basel, Switzerland) for treating renal cell carcinoma, subependymal giant cell astrocytoma associated with tuberous sclerosis, and pancreatic neuroendocrine tumors.³⁶

Given mTOR's central role in multiple cancer-related cellular processes, mTOR inhibition may represent a viable treatment modality in a wide range of tumor types, and many clinical trials are ongoing in various cancer indications. One potential mTOR inhibitor indication that has reached late stages of development is the treatment of estrogen receptor (ER)-positive breast cancer.³⁷

ER-positive metastatic breast cancer often responds to treatment with endocrine therapy; however, most patients' cancers will develop resistance to endocrine therapy.³⁸ Multiple mechanisms of developing resistance to endocrine therapy have been identified, including signaling through the mTOR/phosphatidylinositol-3 kinase (PI3K) pathway.³⁹ Everolimus is being tested as an adjunct to the steroidal aromatase inhibitor exemestane in treating patients whose disease has progressed following treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole).³⁷ Preliminary results from a randomized, double-blind, placebo-controlled clinical trial of 705 patients (BOLERO-2) were published in 2012.⁴⁰ Everolimus (10 mg, daily) met its primary endpoint of improving progression-free survival as determined by investigator assessment (6.9 months vs. 2.8 months; hazard ratio, 0.43; $p < 0.0001$).⁴⁰ Additional late-phase studies of everolimus for use in other breast cancer indications are ongoing.^{41,42} Although results reported from the BOLERO-2 study were promising, it should be noted that an earlier study investigating a combination of the mTOR inhibitor temsirolimus and the aromatase inhibitor letrozole in the first-line treatment of ER-positive, metastatic breast cancer was discontinued after an interim analysis showed that adding temsirolimus to letrozole was unlikely to improve efficacy.⁴³

As a drug class, rapamycin-like mTOR inhibitors have been relatively well tolerated by patients. The prescribing information for everolimus lists the most common side effects observed in patients with breast cancer as follows (in decreasing order of all-grades incidence): stomatitis, infections, rash, fatigue, diarrhea, decreased appetite, nausea, cough, headache, edema, and asthenia.⁴⁴ mTOR inhibition is also associated with renal failure, elevated blood glucose and lipids, and immunosuppression, which can lead to increased risk of infections.^{35,44}

Novartis submitted to FDA a supplemental new drug application (NDA) for everolimus for treating advanced breast cancer in hormone receptor-positive women.⁴⁵ In July 2012, FDA approved everolimus for use in combination with exemestane to treat postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after treatment failure with letrozole or anastrozole.⁴⁶

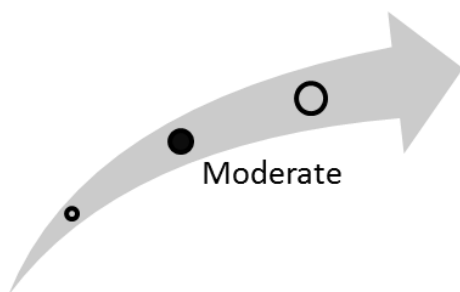
An October 2012 query of an online pharmacy identified a retail price of about \$8,250 per month for everolimus.⁴⁷ Searches of 11 representative, private, third-party payers that publish their

coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 9 payers that include everolimus in their formularies for FDA-approved indications with conditions (i.e., preauthorization, quantity limits, specialty pharmacy dispensing),⁴⁸⁻⁵⁶ and 2 without specific policies.

Clinical Pathway at Point of This Intervention

Patients in whom locally advanced/metastatic ER-positive breast cancer has been diagnosed are typically treated with endocrine therapy using aromatase inhibitors or antiestrogens and may undergo multiple rounds of endocrine therapy. However, a subset of patients with symptomatic disease may be considered for initial treatment with cytotoxic chemotherapy. Patients in whom HER2-negative disease is deemed to have become refractory to endocrine therapy are typically treated with one of several cytotoxic chemotherapy regimens.⁵⁷ Everolimus may be used as an adjunct to the steroidal aromatase inhibitor exemestane in treating patients whose disease has progressed following treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole).³⁷

Figure 2. Overall high-impact potential: everolimus (Afinitor) for treatment of advanced estrogen receptor-positive breast cancer



Experts commenting on this intervention suggested that results for progression-free survival in endocrine-therapy-resistant, metastatic breast cancer were promising for a condition with few treatment options. Experts were anxious to see data showing that the observed improvement in progression-free survival translated to improved overall survival before claiming that mTOR inhibitors would have a large impact on patient outcomes. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of everolimus for treating ER-positive breast cancer.⁵⁸⁻⁶⁴ Experts viewed the unmet need for improved treatments for ER-positive breast cancer resistant to first-line endocrine therapy as moderately to very important, citing the fact that the majority of breast cancers are ER-positive and that most patients with metastatic disease will eventually develop resistance to hormone therapy. Additionally, experts noted that patients with ER-positive metastatic breast cancer resistant to endocrine therapy have a poor prognosis and few treatment options aside from cytotoxic chemotherapy.

The majority of experts believe that everolimus has some potential to improve patient health outcomes. Although experts believe that the progression-free survival benefit demonstrated in the BOLERO-2 trial is significant and suggested that the treatment would likely improve overall

survival, experts believe that any extension of overall survival would likely be of short duration. One clinical expert noted that the toxicity of adding everolimus to endocrine therapy can be significant, citing the five-times-higher rate of treatment discontinuation reported in the everolimus arm of the BOLERO-2 trial. This clinical expert also noted that this positive result for use of an mTOR inhibitor in breast cancer would need to be balanced against the prior negative result for temsirolimus but left open the possibility that patients with hormone-refractory disease represent a subpopulation likely to respond to mTOR inhibition.

Experts suggested that both physicians and patients would likely adopt everolimus to treat endocrine-therapy-resistant breast cancer because of its potential to increase progression-free survival, its oral route of administration, and a manageable side-effect profile relative to cytotoxic chemotherapy. However, several experts noted that the use of everolimus in this setting has not demonstrated an overall survival benefit, which some physicians and patients would like to see before adopting treatment.

The majority of experts suggested that using everolimus to treat endocrine-therapy-resistant breast cancer would lead to a moderate increase in treatment costs. One expert with a clinical perspective noted that if combined treatment with everolimus and exemestane is effective in delaying disease progression, a relatively large population of patients with slowly progressing endocrine therapy-resistant breast cancer could undergo extended treatment with the combination. Two experts, with clinical and research perspectives, suggested that some controversy regarding cost of this therapy could arise if it ultimately fails to demonstrate a significant improvement in overall survival.

Experts did not think that the use of everolimus would have a significant impact on health disparities. However, several experts suggested that an oral route of administration could allow a minor reduction in health disparities if patients who live in remote locations could avoid the need to travel to cancer centers to receive chemotherapy infusions.

As an orally administered medication, everolimus was not anticipated by experts to cause significant shifts in health care staffing or infrastructure or require significant changes in managing patients who would already be closely monitored for disease progression.

MarginProbe System for Intraoperatively Identifying Positive Margins During Breast Cancer Lumpectomy

Successful breast-conserving surgery for early-stage breast cancer requires that the margins around the tissue excised during lumpectomy have cancer-free margins. Many patients who undergo a breast-conserving procedure require a second surgery when postsurgical histopathology identifies that surgical margins are positive for cancer or cancer-free surgical margins are of insufficient depth. A recent observational study of reexcision rates after breast conservation surgery at four institutions calculated an overall reexcision rate of 22.9% and noted that previous studies had reported reexcision rates ranging from 30% to 60%.⁶⁵

The MarginProbe™ System (Dune Medical Devices, Ltd., Caesarea, Israel) is intended for intraoperative assessment of lumpectomy margins to enable breast cancer surgeons to resect additional tissue from positive margins during lumpectomy rather than perform a second procedure at a later date.⁶⁶ Investigators have also begun to test the device for margin assessment in patients undergoing prostatectomy to treat prostate cancer.⁶⁷

The system uses radiofrequency (RF) spectroscopy, in which tissue is subjected to an electromagnetic field to measure its response to stimulation.⁶⁸ Research findings suggest that RF spectroscopy can differentiate between normal and cancerous tissue based on bioelectric differences between the two tissues.⁶⁹ These differences may be due, in part, to changes in the cellular and tissue structure of cancer, including cell membrane depolarization, altered cell nucleus morphology, increased vascularity, and loss of cell-cell adhesion.⁶⁸ Because RF spectroscopy detects tissue response to the electromagnetic field only near the surface of the sample, it is considered appropriate for detecting clean margins, often defined as a depth of normal (noncancerous) tissue of at least 1–2 mm.⁶⁹ The system incorporates a diagnostic algorithm, based on a large number of comparisons between RF spectroscopy readings and pathology results, to differentiate between cancerous and noncancerous tissue.⁷⁰ The system provides a binary (yes/no) answer indicating whether the assessed margin is clean.

In a late-phase trial, the system was used to assess tissue excised from 664 women undergoing lumpectomy procedures to treat nonpalpable malignant lesions that required image-guided localization. Patients were randomly assigned to receive standard intraoperative assessment about whether to resect additional tissue or standard assessment plus use of the system.⁷¹ The primary endpoint was the rate of complete surgical resection (CSR), defined as intraoperative identification of all positive margins and resection of such margins during the lumpectomy procedure.⁶⁶ Preliminary results reported by the manufacturer indicated that the CSR rate was significantly improved in the MarginProbe arm compared with the control arm (72% [117/163] vs. 22% [33/147], $p < 0.0001$). This increase in intraoperative identification of positive margins was reported to have reduced the reexcision rate by about half (5.6% reexcision rate MarginProbe arm; 12.7% in the standard of care arm). Additionally, the volume of tissue dissected in each arm was similar (93 cc MarginProbe arm; 85 cc control arm).⁷¹

In May 2011, Dune Medical announced that FDA had formally accepted the company's premarket approval (PMA) application for the system, which was based on the above trial results.⁷² Given that no device is FDA approved for intraoperative assessment of lumpectomy margins, FDA granted the MarginProbe System priority review. In June 2012, the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee voted in favor of device approval, with the panel voting 11-0 on safety, 8-1 on efficacy (2 abstentions), and 10-1 that its benefits outweigh the risks.^{73,74} In November 2012, Dune Medical announced that it had received an Approvable

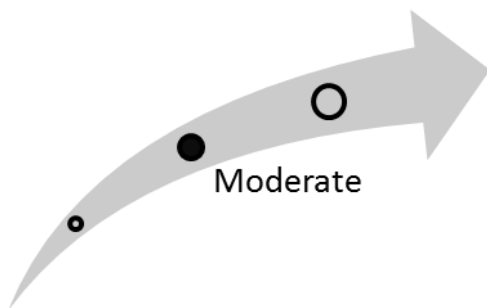
Letter from FDA regarding the premarket approval application for the MarginProbe system.⁷⁵ Final approval is contingent on finalization of the design of a post-approval study of the system. MarginProbe is already available for commercial use in Europe, where the single-use probe used in each MarginProbe procedure costs about 600 euros (\$760).⁷⁶

At least two additional RF spectroscopy and optical spectroscopy devices are under examination in early-phase clinical trials for intraoperatively assessing lumpectomy margins.^{77,78}

Clinical Pathway at Point of This Intervention

The primary treatment for patients in whom early-stage breast cancer (e.g., ductal carcinoma in situ, stage I or II invasive carcinoma of the breast) has been diagnosed is surgical resection of the cancerous tissue. Depending on the stage and level of lymph node involvement, patients may undergo breast-conserving surgery (e.g., lumpectomy) or mastectomy. Alternatively, patients who meet all criteria for breast-conserving surgery except that their tumor is too large may undergo neoadjuvant chemotherapy to reduce tumor size. Following surgical resection, histologic analysis of the resected tissue is performed to assess characteristics of the tumor that may influence subsequent treatment. In particular, lumpectomy samples are tested to assess whether the margins of resected tissue are cancer free. Patients with cancer-positive margins may undergo a subsequent surgical resection to remove additional tissue and establish cancer-free margins. Following lumpectomy, patients are typically treated with radiation therapy or adjuvant systemic therapy (e.g., hormone therapy, chemotherapy) in an attempt to eradicate remaining cancer cells.⁵⁷ If approved, the MarginProbe System would be used during lumpectomy to assess whether lumpectomy margins are cancer free, potentially reducing the need for subsequent surgical procedures.

Figure 3. Overall high-impact potential: MarginProbe System for intraoperatively identifying positive margins during breast cancer lumpectomy



Overall, experts commenting on this intervention believe that a significant unmet need exists for a technology that could rapidly and objectively identify positive margins during breast-conserving surgery, which could significantly reduce the morbidity and costs associated with performing secondary surgeries in this patient population. Although initial results for the MarginProbe system were viewed as promising with limited potential to negatively affect patient outcomes, most experts wanted to see additional data and thought adoption would be limited until then. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁷⁹⁻⁸⁵ The majority of experts agreed that a significant unmet need exists for a technology or methodology that can rapidly assess the margins of excised breast tissue to determine whether further tissue resection is necessary. Experts cited the large number of patients who require

a second surgery following the identification of positive margins during postsurgical histologic analysis and the adverse health effects associated with undergoing a second surgical procedure.

Although experts suggested that filling this unmet need could moderately improve health outcomes for patients by reducing the complications and stress associated with the need to undergo a second lumpectomy or mastectomy, experts were less certain regarding the potential for the MarginProbe System to improve long-term survival for patients with breast cancer. Additionally, experts questioned whether the evidence base for the MarginProbe System was sufficient to suggest that it could meet the unmet need. One expert with a research background questioned whether the device's sensitivity and specificity were sufficient to significantly improve reexcision rates.

The majority of experts did not think that adoption of the MarginProbe system would have a significant impact on health disparities. One expert with a clinical perspective suggested that the system might create a slight increase in health disparities if it were to be offered exclusively at large/high-volume breast cancer centers. Conversely, an expert with a clinical perspective suggested that the system could modestly decrease disparities if it allows less-specialized surgeons to perform breast-conserving surgery in undeserved regions of the country.

Experts agreed that adoption of the system would have minimal impact on health care system staffing and infrastructure. Potential changes such as the need to acquire the system itself, a slight shift in operating room demand due to a small increase in the duration of breast-conservation surgery procedures, and a potential reduction in the number of second surgeries were seen as incremental. Additionally, experts did not think that use of the system would have a significant impact on patient management because patients would follow the same clinical pathway with or without the intraoperative screening with the device.

The majority of experts believe that if final results from the most recent clinical trial of the MarginProbe system demonstrate a clear improvement in the intraoperative detection of positive margins, physicians and patients would rapidly adopt its use to avoid complications associated with reexcision procedures. However, the majority of reviewers thought that more data on the impact of the system on patients with breast cancer would be needed before widespread adoption. Experts also noted that physicians would need to undergo a learning curve in the real-world application of the system; however, multiple clinicians noted that the training required in device use appears likely to be minimal. In terms of patient adoption, experts suggested that the lack of side effects and minimal impact on the patient's care would increase the likelihood for patient adoption.

The majority of experts suggested that the system could have a significant impact by reducing costs associated with breast-conserving surgery. Although initial acquisition of the system and its intraoperative use would likely increase costs, experts suggested that this increase could be outweighed by a reduction in secondary surgery procedures.

Novel Targeted Therapies (Trastuzumab Emtansine; Pertuzumab [Perjeta]) for Advanced HER2-Positive Breast Cancer

HER2-positive breast cancer is a subclass of invasive breast cancer characterized by the expression of high levels of the epidermal growth factor receptor (EGFR) family member HER2, and it comprises approximately 20% of breast cancer cases. Historically, HER2-positive breast cancer has been associated with more aggressive disease and poor outcomes; however, the dependence of HER2-positive breast cancers on HER2 activity for continued proliferation and survival has also provided a clearly defined molecular target.⁸⁶ Indeed, the treatment of HER2-positive breast cancer has improved with the availability of HER2-targeted therapies such as the HER2-specific monoclonal antibody trastuzumab (Herceptin[®]) and the HER2 kinase inhibitor lapatinib (Tykerb[®]); however, many patients' cancers still fail to respond to or progress during these treatments and compounds with improved efficacy and/or efficacy against resistant disease are highly desired.⁸⁷ Two novel biologic therapies are in late-stage clinical trials for treating HER2-positive breast cancer: trastuzumab emtansine and pertuzumab (Perjeta[®]), both developed by F. Hoffmann-La Roche, Ltd. (Basel, Switzerland).

Trastuzumab emtansine (formerly called trastuzumab-DM1), an antibody-drug conjugate (ADC), is an investigational biologic that couples an HER2-specific monoclonal antibody (trastuzumab) to a potent chemotherapeutic agent, the microtubule assembly inhibitor emtansine (DM1).⁸⁸ The antibody and drug are coupled in such a way that emtansine is held in a stable inactive form outside the cell; emtansine is released and activated only upon cellular uptake of the drug conjugate mediated by the antibody's binding to the HER2 receptor.⁸⁸ In this way, the cytotoxic activity of emtansine is targeted to cells expressing the HER2 receptor, preferentially targeting tumor cells (which express high levels of HER2) and sparing many normal tissues from the toxic effects of the cytotoxic drug. Preclinical studies have demonstrated that trastuzumab emtansine retains the antiproliferative activity of trastuzumab, and the cytotoxic activity of emtansine may endow the compound with additional antitumor properties even in tumors that have become independent of HER2 signaling (a hallmark of some tumors that have become resistant to trastuzumab and/or lapatinib).⁸⁷

Trastuzumab-emtansine is being studied in a number of clinical trials in both patients with metastatic disease and patients undergoing adjuvant (postsurgical) chemotherapy. Results have recently been reported from the phase III EMILIA trial, which compared treatment with trastuzumab emtansine to treatment with a standard therapy (lapatinib plus capecitabine) in patients undergoing second-line treatment for metastatic HER2-positive breast cancer. Patients receiving treatment with trastuzumab emtansine demonstrated improved progression-free and overall survival. Median progression-free survival was 9.6 months in the trastuzumab emtansine arm compared with 6.4 months in the lapatinib plus capecitabine arm (hazard ratio [HR]=0.65; 95% confidence interval [CI], 0.55 to 0.77; $p<0.001$), and overall survival at the second interim analysis was 30.9 months in the trastuzumab emtansine arm compared with 25.1 months in the lapatinib plus capecitabine arm (HR=0.68; 95% CI, 0.55 to 0.85, $p<0.001$). Additionally, fewer patients in the trastuzumab-emtansine arm than in the lapatinib-plus-capecitabine arm experienced grade 3 or 4 adverse events (41% in the trastuzumab-emtansine arm vs. 57% in the lapatinib plus capecitabine arm).⁸⁹ Additional phase III trials of trastuzumab emtansine in the first-line and third-line setting are ongoing.

In 2010, Roche submitted a Biologic License Application (BLA) to FDA for using trastuzumab emtansine as third-line treatment (i.e., patients who had undergone at least 2 prior HER2-targeted treatments, typically trastuzumab and lapatinib), based on results from an initial phase II trial.⁹⁰ However, FDA issued Roche a refuse-to-file letter, stating that the trial did not meet the standards for accelerated approval because all potential available treatment options had not been exhausted in the patient population under study.⁹⁰ Subsequently, Roche submitted a BLA based on the results of the phase III EMILIA trial to FDA seeking marketing approval for use of trastuzumab emtansine as a second-line treatment (i.e., patients who had undergone prior treatment with trastuzumab).⁹¹ In November 2012, FDA granted trastuzumab emtansine priority review status and established an action date of February 23, 2013.⁹²

Like trastuzumab, pertuzumab (also being developed by Roche) is a monoclonal antibody specific for the HER2 protein; however, it is purported to inhibit HER2 activity through a mechanism of action different from that of trastuzumab and may act synergistically with trastuzumab treatment.⁹³ Specifically, pertuzumab is intended to block the dimerization of HER2 with HER family receptor tyrosine kinases (e.g., homodimerization with HER2, heterodimerization with HER3), which is required for receptor tyrosine kinase activation.⁹⁴ Pertuzumab is also under study in many stages of breast cancer treatment, including adjuvant therapy for localized disease and first-line treatment for metastatic disease. In 2001, Roche announced positive results from the phase III CLEOPATRA study, which demonstrated that a combination of trastuzumab, docetaxel, and pertuzumab extended progression-free survival compared with trastuzumab, docetaxel, and placebo in chemotherapy-naïve patients with metastatic breast cancer.⁹³ Preliminary results from the trial indicated that adding pertuzumab to a standard first-line therapy for metastatic, HER2-positive breast cancer (trastuzumab plus docetaxel) extended progression-free survival by an average of 6.1 months (18.5 months in the pertuzumab group vs. 12.4 months in the control group).⁹⁵

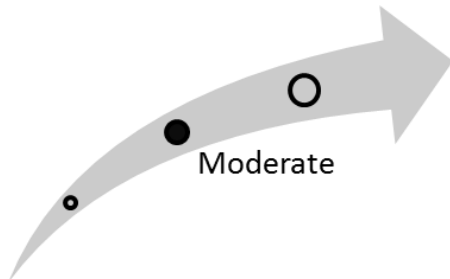
Based on the results of the CLEOPATRA study, a BLA was submitted to FDA and was granted priority review status in February 2012.⁹⁶ In June 2012, FDA approved pertuzumab “for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.”⁹⁷ Pertuzumab became available in August 2012, and by late October of that year was reportedly being used in approximately 30% of eligible patients.^{98,99} Although approximately 40% of oncologists were reported as having prescribed pertuzumab at least once, a survey of 74 oncologists indicated that key barriers to increased use of pertuzumab included “concerns over cardiotoxicities, lack of finalized overall survival data, and increased cost.”⁹⁸ Although the reported wholesale acquisition cost for one patient for a month of pertuzumab is \$5,900, similar to other recently approved anti-cancer agents, the on-label use of pertuzumab in combination with trastuzumab could push the cost of a typical course of treatment to approximately \$187,000.¹⁰⁰

Clinical Pathway at Point of This Intervention

Patients with HER2-positive breast cancer that is locally advanced or has become metastatic and is untreatable by surgical resection are typically treated using a series of HER2-targeted therapies. Standard first-line therapy typically includes treatment with trastuzumab plus a single cytotoxic chemotherapy agent (e.g., capecitabine, docetaxel, paclitaxel, vinorelbine). Patients whose disease progresses following first-line therapy are typically treated with a second HER2-targeted therapy, typically lapatinib plus capecitabine. Alternative second-line chemotherapy options include trastuzumab plus a cytotoxic agent that was not used in first-line treatment or trastuzumab plus lapatinib.⁵⁷ The most advanced phase III clinical trial of trastuzumab emtansine is studying the drug

as a second-line treatment option that could displace the use of current treatments. The most advanced phase III clinical trial of pertuzumab is studying the drug as a first-line treatment that would be used in conjunction with standard first-line therapy.

Figure 4. Overall high-impact potential: novel targeted therapies (trastuzumab emtansine; pertuzumab [Perjeta]) for advanced HER2-positive breast cancer



Overall, experts commenting on these interventions believe that trastuzumab emtansine and pertuzumab have significant potential to incrementally improve existing HER2-positive metastatic breast cancer treatments, the shortcomings of which they thought represented a significant unmet need. Experts also thought that trastuzumab emtansine's potential to displace current standard-of-care treatments for HER2-positive metastatic breast cancer and likely high cost of both trastuzumab emtansine and pertuzumab could have significant impacts on managing these patients. Based on this input, our overall assessment is that these interventions are in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on trastuzumab emtansine for treating breast cancer.¹⁰¹⁻¹⁰⁷ Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on pertuzumab for treating breast cancer.¹⁰⁸⁻¹¹⁴ It should be noted that experts provided comments on these interventions before the recent release of phase III data. At the time of review, Roche had not yet announced that the phase III trial of trastuzumab emtansine in second-line treatment of metastatic breast cancer had met its primary endpoint. Similarly, although Roche had announced that the phase III trial of pertuzumab in first-line treatment of metastatic breast cancer had met its primary endpoint, the magnitude of the improvement in progression-free survival had not yet been released.

The majority of experts agreed that a significant unmet need exists for improved treatments of HER2-positive metastatic breast cancer, citing the fact that many patients have disease that is refractory to current therapies and/or progresses during therapy. Although experts believe the overall unmet need in HER2-positive breast cancer is large, they were less enthusiastic about the use of these novel agents in salvage settings after treatment with any of a number of first-line regimens.

Based on the results of the phase II trials, the majority of experts thought that trastuzumab emtansine has moderate to large potential to improve patient health. Experts thought that the phase II trial results suggested that trastuzumab emtansine might improve on both the efficacy (i.e., ability to improve progression-free survival) and safety of current HER2-targeted therapies; however, experts seemed to believe that the improvements relative to the efficacy of current treatments for HER2-positive metastatic disease would likely be incremental, especially in the third-line refractory disease setting. Multiple experts noted that if trastuzumab emtansine were shown to improve

outcomes in the first-line metastatic disease or adjuvant setting, it could have a more significant impact on HER2-positive disease treatment models.

Similarly, the majority of experts thought that pertuzumab has moderate to large potential to improve patient health, citing the preliminary signals of activity in the neoadjuvant setting (i.e., presurgical treatment of localized disease) and heavily pretreated patients. Two experts (both with a research perspective) thought that pertuzumab has only minimal potential to improve patient health, suggesting that the addition of pertuzumab to current treatment of HER2-positive breast cancer would represent only an incremental improvement on existing therapies. Multiple experts mentioned the potential for cardiac toxicity known to be associated with trastuzumab treatment and suggested that further study of the drug would need to rule out the possibility of cumulative heart damage due to multiple antibodies simultaneously targeting HER2 or prolonged duration of anti-HER2 therapy.

Because health care workers would administer trastuzumab emtansine and pertuzumab in the same manner as existing HER2-targeted therapies (e.g., trastuzumab), experts did not think that adoption of the drugs would require significant changes in health care facility staffing or infrastructure. As such, experts saw few obstacles to patients or physicians adopting the use of trastuzumab emtansine and pertuzumab. One potential obstacle raised by experts was the likely high cost of trastuzumab emtansine and pertuzumab, which could affect patient out-of-pocket costs. Additionally, experts noted that the likely high cost of these drugs has the potential to be controversial in terms of the cost-benefit ratio and has the potential to increase health disparities.

Colorectal Cancer Interventions

Concomitant Colorectal Cancer Screening and Annual Influenza Vaccine (FLU-FOBT) Program

Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States.¹¹⁵ CRC tends to be slow to develop, and precancerous lesions and early-stage CRCs can typically be treated successfully by surgical resection. Therefore, successful CRC screening programs could mitigate much of the morbidity and mortality associated with this condition. However, with current screening options, only a minority of the population adheres to CRC screening guidelines, and about half of CRCs diagnosed in the United States are diagnosed at late disease stages.^{115,116} Therefore, programs, such as FLU-FOBT (fecal occult blood testing), that have the potential to improve CRC screening rates are highly sought.

Multiple barriers to CRC screening have been cited, including patient-specific barriers and health care system barriers.¹¹⁷ Patient-specific barriers include lack of patient awareness of the screening benefits and recommendations, embarrassment over the nature of screening methods, anxiety regarding screening, and cost, especially for patients lacking health insurance coverage.¹¹⁸ Health care system barriers include the lack of time to address all aspects of a patient's health during primary care appointments, a lack of reminders that a patient is due for screening, an inability to track down dates of prior screening, and long delays in colonoscopy scheduling and/or lack of direct access to colonoscopy.¹¹⁹

One proposed solution for providing timely and routinized CRC screening is the pairing of FOBT or fecal immunochemical testing (FIT) with annual influenza immunization.¹¹⁷ Influenza immunization and FOBT/FIT share several attributes that could make them highly complementary: both are recommended to be performed annually and both are, at least in part, targeted to elderly patients. The University of California, San Francisco (UCSF) has implemented versions of this program within various settings, including influenza vaccine clinics (both hospital-based and managed-care-based), pharmacy-based influenza vaccination campaigns, community health care clinics, and primary care centers.^{117,120-123}

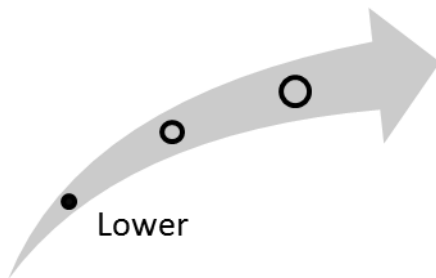
Hallmarks of the UCSF studies included provision of home FOBT/FIT kits to patients whose medical records indicated that they were due for CRC screening, provision of a multilingual information pamphlet on the benefits of CRC screening, training of health care workers in culturally sensitive discussion of CRC screening, and followup telephone calls to patients who had received FOBT/FIT test kits but did not return samples.¹¹⁷

In the largest test of the concept to date, patients obtaining influenza vaccinations at a high-volume influenza clinic run by a managed care organization were randomly assigned to receive either the influenza vaccination alone (n=4,653) or the influenza vaccine as well as an FIT test kit (n=2,182). Within 3 months of their visit to the influenza clinic, 13.7% of patients in the influenza vaccine-only cohort completed a FIT test compared with 30.3% of patients in the influenza vaccine plus FIT test kit cohort. The percentage of patients adhering to CRC screening recommendations increased from 51.5% to 56.3% in the influenza-only group compared with 49.2% to 63.2% in the influenza vaccine plus FIT test kit cohort (p < 0.0001 for the change difference between cohorts).¹²⁰ A study of the FLU-FOBT program 1 year following its initial implementation revealed that 63% of clinics continued to offer FOBT with the influenza vaccines and 85% of clinics continued to provide mailing kits with FOBT.¹²⁴

Current Approach to Care

Several options are used for routine CRC screening in the general population that has an average risk of developing CRC. These include annual FOBTs, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, computed tomography colonography every 5 years, or colonoscopy every 10 years.¹²⁵ Patients typically engage the health care system during primary care visits, during which caregivers can advise patients of the potential benefits of CRC screening.¹¹⁷ Additionally, national campaigns such as the U.S. Centers for Disease Control and Prevention's Screen for Life program disseminate information on CRC that may influence an individual's decision to seek CRC screening.¹¹⁶

Figure 5. Overall high-impact potential: concomitant colorectal cancer screening and annual influenza vaccine (FLU-FOBT) program



Experts who commented on this topic believe that it has an interesting approach to increasing CRC screening rates that has significant potential to improve screening adherence in certain settings. However, experts questioned whether such a program could be implemented on a large scale, thereby limiting their view of its overall potential for high impact. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.¹²⁶⁻¹³² Experts were of the opinion that programs linking routine CRC screening with the annual administration of influenza vaccines have the potential to address a moderately to very important unmet need, citing low adherence rates to CRC screening guidelines in spite of evidence of their ability to reduce CRC-associated mortality. However, several experts noted that the ability of such a program to reach unscreened patients could be limited by the extent to which patients who do not adhere with CRC screening seek annual influenza vaccination. In this vein, experts noted that patients seeking prophylactic vaccination for influenza might be more likely than the average patient to already be adhering to preventive screening measures such as CRC screening. However, to the extent that patients who were not up to date with CRC screening were reached by such a program, it has significant potential to improve CRC screening rates and, therefore, improve patient health, experts thought.

Experts were divided on whether the FLU-FOBT program has potential to improve health disparities. Those who thought the program could improve disparities cited the emphasis placed on cultural sensitivity in the pilot programs, which could influence patients in certain underserved populations who previously resisted discussing or undergoing CRC screening to do so. These experts also noted the diversity of settings in which the program was offered (e.g., managed care clinics, pharmacies, community health care clinics), which could reach some underserved patients who do not routinely see a primary care physician. Conversely, experts who did not think the FLU-

FOBT program would have a significant impact on health disparities questioned whether patients who typically resist undergoing CRC screening could be convinced to do so and suggested that fewer patients in traditionally underserved populations would routinely seek vaccination against influenza.

Although implementing the FLU-FOBT program could shift the care setting for disseminating information about CRC screening and would necessitate some training of health care facility staff, it would not likely have a significant impact on health care infrastructure or patient management, experts believe. However, multiple experts noted the need to follow up with patients receiving positive results from noninvasive tests, which could represent a significant shift in the way patients are otherwise managed, especially for FLU-FOBT programs implemented in settings that are not associated with a gastroenterologist (e.g., pharmacies).

Experts disagreed on whether health care workers would accept and adopt the implementation of a FLU-FOBT program. Although some experts suggested that clinicians would welcome an innovation that might increase CRC screening rates, others suggested that clinicians may not want to spend the time providing information about CRC screening in what are presumably high-volume settings. Additionally, several experts noted that patients often fail to return FOBT test kits, and health care systems might not want to allocate time and resources to follow up with patients to encourage them to return the kits.

Methylated Septin 9 Blood Test for Colorectal Cancer Screening

CRC is the third most common cancer diagnosed in the United States.¹¹⁵ CRC tends to be slow to develop, and precancerous lesions and early-stage CRCs can typically be treated successfully by surgical resection. Therefore, successful CRC screening programs could mitigate much of the morbidity and mortality associated with this condition. However, with current screening options, only a minority of the population adheres to CRC screening guidelines, and about 50% of CRCs diagnosed in the United States are diagnosed at late disease stages.¹¹⁵ Therefore, new screening methodologies that could increase the percentage of the population that undergoes recommended CRC screening are highly sought.

Research has demonstrated that cells undergo a range of epigenetic modifications (e.g., DNA methylation) during their transformation to cancerous cells.¹³³ Additionally, elevated levels of methylated DNA have been found in the blood of patients with CRC, which could serve as a readily accessible marker for cancer screening.¹³³ One methylated DNA species that has been shown to be present specifically in the blood of individuals with CRC is a methylated form of the Septin 9 gene, detection of which is being studied as a potential colon cancer screening test.¹³³ Like other noninvasive colon cancer tests (e.g., FOBT), a positive result from the methylated Septin 9 test would require that the patient undergo a colonoscopy to confirm the result and resect any precancerous or cancerous lesions.¹³⁴

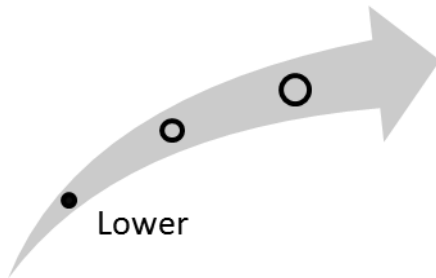
A methylated Septin 9 DNA blood test is being developed by Epigenomics AG (Berlin, Germany). In December 2011, Epigenomics released initial data from a trial in which a subset of 7,940 patients undergoing colonoscopy screening were also tested with the Epigenomics Septin 9 test.^{135,136} Blood samples were collected from all patients who subsequently underwent colonoscopy for determination of CRC status. A subset of these samples was tested using the Epi proColon 2.0 blood test. Tested samples included those from all 50 patients with CRC, all 650 patients with advanced adenomas, a random subset of 450 patients with small polyps, and a random subset of 450 patients with no evidence of CRC. Preliminary results indicated that, compared with CRC detection by colonoscopy, the Septin 9 test had a sensitivity of 68% and a specificity of 80%.¹³⁶ Data on the test's ability to detect precancerous adenomatous polyps were not presented.

As of September 2012, Epigenomics had submitted the first three portions of a modular premarket approval application (PMA) to FDA, intending to complete the PMA application by the end of 2012.¹³⁷ The fourth module will include data from an ongoing head-to-head trial¹³⁸ of Epi proColon 2.0 and FIT designed to demonstrate noninferiority of the Epi proColon 2.0 test.^{137,139}

Clinical Pathway at Point of This Intervention

Several options are available for routine CRC screening in patients with an average risk of developing colon cancer, including annual FOBTs, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, computed tomography colonography every 5 years, or colonoscopy every 10 years.¹²⁵ For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and perform any required biopsy of suspicious polyps.¹²⁵ Septin 9 blood testing would be another routine screening option that, like other noncolonoscopic methods, would require a followup colonoscopy for positive result confirmation and lesion excision.¹³⁴ Information on the test states that it is not intended to substitute for colonoscopy; however, it might be useful as a complement to colonoscopy or for use in individuals unwilling or unable to undergo colonoscopy.¹⁴⁰ For those individuals, it might also be a useful screening tool.

Figure 6. Overall high-impact potential: Methylated Septin 9 blood test for colorectal cancer screening



Overall, most experts commenting on this intervention thought that an accurate blood-based CRC screening test obtained through venipuncture (rather than testing a stool sample) could fundamentally change CRC screening practices by increasing the percentage of patients screened for CRC. However, regarding the Epi proColon 2.0 test specifically, experts were more cautious, questioning whether the reported sensitivity and specificity of the test were high enough and whether the likely high cost of the test relative to other noninvasive options such as FOBTs would prevent its widespread adoption. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.¹⁴¹⁻¹⁴⁷ The majority of experts thought that a blood-based screening technology has the potential to address a significant unmet need, citing the current lack of such tests and the low rate of adherence to recommended screening (i.e., fecal sample testing, colonoscopy, colonography) that may be due, in part, to discomfort with current test methods. One researcher saw a more limited unmet need, stating that multiple noninvasive tests are already available for CRC and that the Septin 9 test would provide only another such option. Other experts saw more significance in the blood-based nature of the test, stating that it would likely be more acceptable to patients than current noninvasive fecal-based tests and that patients who were unwilling to undergo screening might do so. Additionally, multiple experts noted that the blood-based nature of the test could allow its incorporation into routine blood tests (e.g., cholesterol screening). In this way, experts thought the Septin 9 blood test has potential to shift patterns of patient management significantly by allowing primary care physicians to incorporate noninvasive CRC screening into routine care rather than requiring patients to return fecal samples collected in the home setting. Based on the potential that a blood-based test could increase screening rates (particularly among individuals who are not undergoing any screening), experts believe that the Septin 9 screening test could lead to significant improvement in patient health outcomes. However, multiple experts expressed concern regarding the reported sensitivity and specificity of the Epi proColon test and noted that false-negative results of the Septin 9 test could lead to significant disease progression before detection. One expert with a clinical perspective suggested that the potential for false-negative results could be most relevant if some patients opt for the convenience of an available blood test over colonoscopy.

The majority of experts noted that the Septin 9 test was significantly more expensive than noninvasive fecal tests (e.g., FOBT, FIT). Although the frequency with which the Septin 9 test would need to be performed has not yet been determined, multiple experts suggested that screening a large number of patients with the Septin 9 test would significantly increase the cost of CRC

screening. Ultimately, cost-effectiveness studies are needed to determine whether sufficient numbers of treatable CRCs could be identified to offset the cost of screening.

Hematologic Malignancy Interventions

Brentuximab Vedotin (Adcetris) for Recurrent or Treatment-Refractory Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma

CD30 is a defining marker of Hodgkin's lymphoma (HL) and anaplastic, large cell lymphoma (ALCL).¹⁴⁸ Both HL and ALCL are rare, with about 8,500 cases of HL and 2,250 cases of ALCL diagnosed annually in the United States.^{148,149} Although many patients achieve complete remission following standard treatments for HL and ALCL, a significant proportion has disease that is refractory to standard therapies or recurs after first-line treatment. Available treatments for recurrent or refractory HL and ALCL provide little benefit to affected patients, and no consensus exists on optimal treatment of these patients.¹⁴⁸

Brentuximab vedotin (Adcetris[®]) is an ADC targeted to CD30 that has been developed for treating patients with recurrent or refractory HL or ALCL.¹⁴⁸ The biologic compound consists of a CD30-specific monoclonal antibody chemically conjugated to a potent, chemotherapeutic agent, monomethyl auristatin E (MMAE).¹⁵⁰ Brentuximab vedotin is intended to target CD30-expressing cells and contains a novel peptide-based linking system designed to allow it to remain stable in the bloodstream and only release the cytotoxic MMAE upon ADC internalization by cells.¹⁵¹ By targeting the cytotoxic molecule to CD30-expressing tumor cells, brentuximab vedotin is purported to minimize systemic toxicity while focusing cytotoxic effects on the target tumor.

Seattle Genetics, Inc. (Bothell, WA), in collaboration with the Millennium Pharmaceuticals subsidiary of Takeda Pharmaceutical Co., Ltd. (Osaka, Japan), developed the agent. Treatment consists of an intravenous infusion of 1.8 mg/kg of body weight every 3 weeks for up to 16 total doses.¹⁵² Common adverse effects reported in trials included diarrhea, fatigue, nausea, neutropenia, peripheral neuropathy, and pyrexia, which were characterized as "manageable."^{153,154} Since the trials, three cases of progressive multifocal leukoencephalopathy, a brain infection that can result in death, have been reported in patients who were undergoing brentuximab vedotin treatment.¹⁵⁵

Researchers have reported results from two open-label, single-group assignment, phase II clinical trials: one trial in patients with relapsed or refractory HL and the other in patients with relapsed or refractory ALCL. In the trial of patients with relapsed or treatment-refractory HL (n=102), the overall response rate as assessed by an independent review facility was 75%, and 34% of patients achieved complete remission. The median response duration was 5.6 months as assessed by independent central review, and among patients achieving a complete remission, the median response duration was reported to be 20.5 months.¹⁵¹ In the clinical trial of the agent in patients with relapsed or treatment-refractory ALCL (n=58), the overall response rate as assessed by an independent review facility was 86%, and 53% of patients achieved complete remission. The median response duration had not been reached when results were released and ranged from 0.3 to 45.3 weeks.¹⁵⁶

Seattle Genetics owns commercialization rights for brentuximab vedotin in the United States and Canada. After granting the agent orphan drug designation in 2007 and fast track status in 2009, FDA granted the drug accelerated approval in August 2011 for treating both HL and ALCL.¹⁵⁷ The approved indications are for patients with HL who have failed to respond to an autologous stem cell transplantation or whose disease has progressed after at least two multiagent chemotherapy regimens and who are not autologous stem cell transplant candidates and for patients with ALCL after failure of at least one multiagent chemotherapy regimen.^{157,158}

The initial drug pricing was set at about \$4,500 per vial with about three vials used per treatment and 7–9 cycles of treatment given per patient, bringing the total cost for a complete regimen to \$94,000 to \$121,000.¹⁵⁹ In July 2012, the company announced a 3.5% price increase.¹⁶⁰

Among 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), all identified policies (6 payers) covered the use of brentuximab vedotin in the FDA-approved indications.¹⁶¹⁻¹⁶⁶ Since the launch of brentuximab vedotin, Seattle Genetics has reported that it is not aware of any refusals to reimburse an on-label use of the drug.¹⁶⁷ Seattle Genetics has a patient assistance program that may provide assistance to both uninsured and underinsured patients as well as assistance with coinsurance payments.¹⁶⁸

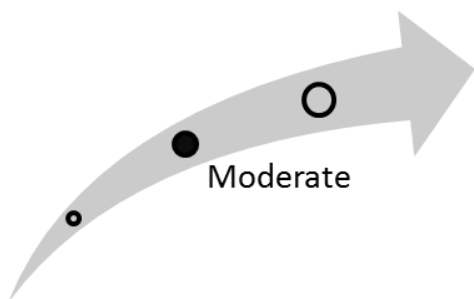
Potential exists for using brentuximab vedotin to expand beyond the FDA-approved indications. Early-phase clinical trials incorporating brentuximab vedotin into first-line chemotherapy regimens for treating HL and ALCL are ongoing.^{169,170} Reports on the preliminary diffusion of brentuximab vedotin indicate that physicians are prescribing the drug as a bridge to transplant in patients with HL in addition to its FDA-approved indication (i.e., post-transplant or transplant-ineligible HL).¹⁶⁷ Lastly, brentuximab vedotin is also being studied in treating other CD30-positive malignancies (e.g., CD30-positive cutaneous T-cell lymphoma).¹⁷¹

Clinical Pathway at Point of This Intervention

Standard treatment for HL consists of chemotherapy, involved-field radiation therapy, extended-field radiation therapy, and combined modality treatment. Common chemotherapies used in combined modality treatment include ABVD (adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) and Stanford V (mechlorethamine, doxorubicin, etoposide, vinblastine, vincristine, bleomycin, and prednisone).¹⁴⁹ Patients whose disease progresses following first-line therapy may undergo subsequent treatment with radiation therapy, high-dose chemotherapy coupled with autologous stem cell transplantation, or one of a range of salvage chemotherapy regimens.¹⁴⁹

Patients in whom ALCL has been diagnosed typically undergo first-line therapy with an anthracycline-based chemotherapy combination, most commonly CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).¹⁷² Some patients, in particular patients with anaplastic lymphoma kinase (ALK)-negative disease, may undergo consolidation chemotherapy consisting of a high-dose chemotherapy regimen with stem cell rescue.¹⁷² No consensus treatment has been established in patients who do not respond to first-line therapy or have recurrent disease following first-line treatment; however, patients are typically treated with a new chemotherapy regimen, including EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), ESHAP (etoposide, methylprednisone, cytarabine, cisplatin), or ICE (ifosfamide, carboplatin, etoposide).^{148,172}

Figure 7. Overall high-impact potential: brentuximab vedotin (Adcetris) for recurrent or treatment-refractory Hodgkin's lymphoma or anaplastic large cell lymphoma



Overall, experts commenting on this intervention believe that the potential impact of brentuximab vedotin is high as a novel ADC that may have the potential to effectively treat CD30-

positive malignancies that are refractory to standard therapies and have few treatment options. However, the overall impact on the health care system would be limited by the routine manner of administration and the relatively small patient population affected by these conditions. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on use of brentuximab vedotin.¹⁷³⁻¹⁷⁸ Overall, experts concurred that the lack of efficacious treatments for these cancers represents an important unmet need for new treatment options. All but one expert thought that the available data suggested that brentuximab vedotin has significant potential to improve health outcomes of patients with HL, citing the high response rate observed in the clinical trial and the fact that no other therapy has shown a significant benefit in this patient population. However, several experts noted that the completed trials were single-arm clinical trials that reported only a response rate, and so a clear survival benefit had not yet been demonstrated.

Despite the preliminary nature of the data, the majority experts thought that brentuximab vedotin would be widely accepted by both patients and clinicians because of the lack of effective treatment options for patients with HL and the high response rate reported in trials. Multiple experts also cited the brentuximab vedotin's relatively benign adverse event profile as another factor influencing physician and patient adoption; however, a few experts suggested that the reports of high rates of peripheral neuropathy and rare cases of progressive multifocal leukoencephalopathy could discourage physicians and patients from opting for the treatments.

All experts agreed that brentuximab vedotin would increase the cost of care because it would be additive to the current clinical pathway for HL. Multiple experts suggested that the high cost of brentuximab vedotin could potentially make the drug inaccessible to underserved patients, possibly worsening existing health disparities. Although all experts indicated that they believe brentuximab vedotin would lead to increased costs, multiple experts suggested that further studies could lead to the use of brentuximab vedotin earlier in the treatment pathway and, if this adoption improves long-term response rates, it could limit downstream costs associated with expensive second-line therapies such as autologous stem cell transplantation.

Six experts, with clinical, research, and health systems backgrounds, offered comments on using brentuximab vedotin to treat ALCL.¹⁷⁹⁻¹⁸⁴ Experts were unanimous in their opinion that patients with ALCL whose cancer failed to be cured by first-line chemotherapy (and in some cases, stem cell transplantation) have few effective treatment options and a poor prognosis; therefore, this disease setting represents a significant unmet need. However, the majority of experts also noted that ALCL is a rare condition, which would limit potential impact of this therapy on the overall health system.

The majority of experts believe that the high response rates demonstrated in the phase II trial in patients with treatment-refractory ALCL suggests that brentuximab vedotin has significant potential to improve patient health outcomes. However, multiple experts noted that longer-term, followup data are needed to determine whether these responses are durable. Additionally, several experts suggested that the lack of a control arm in the trial made it difficult to assess the response rates. With those data limitations in mind, one expert with a research background suggested that brentuximab vedotin has only minimal potential to improve patient health outcomes, compared with salvage therapy options.

Experts did not think that an intravenously administered chemotherapy drug used in a patient population that has likely already undergone prior rounds of intravenous therapy would necessitate

significant changes in health care facility staffing or infrastructure or in the manner in which patients with ALCL are managed. However, one expert with a clinical background suggested that brentuximab vedotin could alter the continuum of care for ALCL if it is shown to be safe and effective in first-line disease treatment.

Experts were unanimous in their opinion that both physicians and patients would be highly likely to adopt the use of brentuximab vedotin for treating ALCL, citing the lack of alternatives demonstrating efficacy in refractory ALCL and the encouraging response rates reported in the clinical trial. Additional factors noted by experts as influencing adoption included the routine and familiar route of administration and the relatively benign side-effect profile. Like experts commenting on the use of brentuximab vedotin for treating HL, experts suggested that reports of high rates of peripheral neuropathy and sporadic reports of progressive multifocal leukoencephalopathy could discourage some patients from opting for brentuximab vedotin treatment.

Although all experts noted the high cost of brentuximab vedotin treatment per patient, many suggested that the impact on overall health care system costs would be limited by the small number of patients with ALCL who would receive the treatment.

Ruxolitinib (Jakafi) for Treatment of Myelofibrosis

Myelofibrosis is one of three closely related disorders (i.e., myelofibrosis, polycythemia vera, essential thrombocythosis) caused by abnormalities in the myeloid hematopoietic lineage that lead to clonal expansion of a myeloid progenitor cell. One of the primary symptoms of myelofibrosis is splenomegaly (i.e., enlarged spleen) caused by abnormal myeloid cells accumulating in the spleen.¹⁸⁵ Current treatments for myelofibrosis are largely palliative, and novel treatments are needed.

One molecular target that may be amenable to pharmaceutical intervention for treating myelofibrosis is the JAK/STAT pathway. JAK/STAT activity has been implicated in the clonal proliferation of myeloid progenitor cells that leads to myelofibrosis. In particular, genetic mutations that lead to JAK/STAT pathway activation (e.g., activating mutations in JAK2, a tyrosine kinase that functions in the JAK/STAT pathway) have been identified in about two-thirds of myelofibrosis cases.^{186,187} Besides a potential role in driving clonal proliferation, JAK/STAT signaling may also play a role in the elevated levels of proinflammatory cytokines observed in myelofibrosis and that probably contribute to disease symptoms.¹⁸⁸ JAK/STAT signaling is known to be involved in both producing proinflammatory cytokines and mediating the effects of cytokines in target cells; therefore, inhibition of JAK kinases also has the potential to improve myelofibrosis symptoms by limiting inflammation.¹⁸⁸

Ruxolitinib (Jakafi[®]) is a small-molecule kinase inhibitor that has activity against both JAK1 and JAK2 tyrosine kinases and represents the first JAK/STAT pathway inhibitor for treating myelofibrosis.¹⁸⁹ Ruxolitinib was developed by Incyte Corp. (Wilmington, DE) in cooperation with Novartis International AG (Basel, Switzerland), which holds rights to the compound outside the United States.¹⁹⁰

Ruxolitinib has been studied in two phase III clinical trials (COMFORT-I and COMFORT-II). In COMFORT-I, the safety and efficacy of treating patients with myelofibrosis using ruxolitinib (n=155) was compared with using placebo (n=154).¹⁹¹ In results published in 2012, investigators reported that 41.9% of patients in the ruxolitinib arm achieved a 35% or more reduction in spleen size at 24 weeks compared with 0.7% of patients in the placebo arm ($p<0.001$).¹⁹¹ In COMFORT-II, the safety and efficacy of treating patients who had myelofibrosis with ruxolitinib (n=146) was compared with best alternative therapy consisting of another agent or no treatment (n=73).¹⁹² In results published in 2012, researchers reported 28% of patients in the ruxolitinib arm exhibited a 35% or more reduction in spleen size at 48 weeks versus 0% of patients in the best alternative therapy arm ($p<0.001$).¹⁹²

Adverse events were reported as more common in the ruxolitinib arms of the two trials compared with the placebo or best alternative therapy arms.^{191,192} The most common adverse events included anemia, diarrhea, peripheral edema, and thrombocytopenia. Grade 3 or 4 adverse events were observed in fewer than 10% of patients treated with ruxolitinib and included anemia and thrombocytopenia, which may require blood transfusions.¹⁹³ Besides adverse events observed during treatment, instances of serious adverse events (e.g., acute relapse of symptoms, rapid and painful spleen enlargement, acute hemodynamic decompensation) have been reported following discontinuation of ruxolitinib treatment.¹⁸⁸

In November 2011, FDA approved ruxolitinib for treating intermediate- or high-risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis).^{193,194} Incyte set the retail price of ruxolitinib at \$7,000 for 1 month of treatment.¹⁹⁵ The drug is listed as a specialty pharmaceutical with most third-party payers and typically requires prior authorization. The initial uptake of ruxolitinib for treating

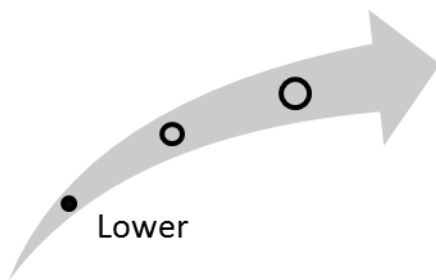
patients with myelofibrosis has been reported as rapid, which has been attributed to “high physician awareness, limited reimbursement pushback, and strong patient demand.”¹⁹⁶

Ruxolitinib is under study in a phase III trial for treating polycythemia vera as well as earlier-phase trials for other hematologic malignancies.¹⁹⁷

Clinical Pathway at Point of This Intervention

Following diagnosis of a myelofibrosis disorder, symptomatic patients may undergo palliative treatments such as blood transfusions or androgen therapy (for anemia), hydroxyurea chemotherapy, radiation therapy, combination thalidomide and prednisone treatment, or splenectomy.¹⁹⁸ Patients may also undergo allogeneic stem cell transplantation to attempt to cure the condition.¹⁹⁸ Ruxolitinib represents an additional treatment option for patients with myelofibrosis.

Figure 8. Overall high-impact potential: ruxolitinib (Jakafi) for treatment of myelofibrosis



Overall, experts believe that ruxolitinib addresses a significant unmet need for novel treatments for myelofibrosis and that the mechanism of action of ruxolitinib is highly suited to this indication. Although experts believe that it would likely be adopted by physicians and patients based on encouraging data regarding spleen size, experts were cautious, given the lack of data on patient survival and disease progression. Lastly, experts did not think that the oral medication, intended for use in a relatively small patient population, would significantly affect the health care system. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.¹⁹⁹⁻²⁰⁵ Experts concurred that a significant unmet need exists in the treatment of myelofibrosis, citing the lack of FDA-approved therapies for this condition and the inadequacy of current treatments. Experts also believe that the purported mechanism of action of ruxolitinib, in particular its activity against JAK2, was a highly logical approach to treating this condition. Although experts had positive opinions about the available data on ruxolitinib’s effectiveness, multiple experts noted that ruxolitinib had demonstrated an effect only on spleen size and that its long-term effects on patient survival and disease progression were unknown. Still, given the lack of effective myelofibrosis treatment options, the majority of experts believe that ruxolitinib would displace current therapies for many patients in whom myelofibrosis has been diagnosed.

As an oral medication that would be used to treat a relatively rare disease, ruxolitinib was not expected by the experts to have a significant impact on health care staffing or infrastructure. Similarly, the majority of experts did not envision an oral medication such as ruxolitinib causing significant shifts in health care processes or health care setting.

The majority of experts agreed that patients and physicians alike would be likely to adopt ruxolitinib, citing the lack of effective alternative therapies and the ease and convenience of prescribing and taking an oral medication. Multiple experts with clinical backgrounds cautioned that it may not initially be clear whether ruxolitinib would be indicated for all patients with myelofibrosis, which may slow physician adoption. One clinical expert also noted that ruxolitinib would likely be a highly expensive drug, which, depending on insurance coverage and reimbursement policies, may restrict patient use. A second clinical expert noted that up to 10% of patients experienced severe adverse reactions while using ruxolitinib, which might dissuade some patients from opting for the treatment, especially if no impact on survival or disease progression is observed. Citing the lack of data on ruxolitinib's effect on survival, multiple experts suggested that the cost-benefit ratio for this therapy has the potential to generate some controversy if it is seen as only a palliative therapy.

Multikinase Inhibitor (Ponatinib) for Treatment of Chronic Myelogenous Leukemia or Philadelphia-Chromosome-Positive Acute Lymphoblastic Leukemia

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder that typically progresses through three phases—chronic, accelerated, and blast—that are characterized by increasing numbers of immature blood cells (i.e., myoblasts or blasts) in the blood and bone marrow.^{206,207} Although patients with chronic-phase CML typically have mild symptoms (e.g., fever, poor appetite, weight loss) and their disease often responds to treatment, patients in more advanced phases typically have more pronounced symptoms and their disease responds less well to treatment. CML in blast crisis behaves more like an acute leukemia than a chronic leukemia and requires aggressive treatment. The majority (85%) of patients receive the diagnosis of CML when they are in the chronic phase.²⁰⁸

CML's defining feature is a specific genetic mutation, a genetic fusion between the breakpoint cluster region (BCR) of chromosome 22 and the Abelson kinase (*ABL*) oncogene on chromosome 9.²⁰⁸ The majority of BCR-ABL gene fusions result from a reciprocal translocation between the long arm of chromosome 22 and the long arm of chromosome 9, a cytogenic abnormality known as the Philadelphia chromosome.²⁰⁷ The protein kinase expressed by the *BCR-ABL* gene is constitutively active and drives the pathogenesis of CML.²⁰⁷ About 25% of cases of another type of leukemia, acute lymphoblastic leukemia (ALL) also involve the *BCR-ABL* oncogene.²⁰⁹ ALL typically progresses rapidly and can be lethal within months in the absence of aggressive treatment. Historically, Philadelphia-chromosome-positive ALL (Ph+ ALL) has been associated with a worse prognosis than Philadelphia chromosome-negative ALL.²¹⁰

The availability of tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, and nilotinib that target the oncogenic BCR-ABL kinase has significantly improved the prognosis for patients with CML.²¹¹ However, although many patients have long-term responses to ongoing TKI treatment, no treatment options are available for patients who fail to respond to available TKIs or develop resistance to them. In particular, CML with the threonine 315 to isoleucine (T315I) mutation in the BCR-ABL kinase is resistant to all available TKIs.²¹¹ Ponatinib is a novel BCR-ABL inhibitor that has demonstrated activity against resistant forms of CML, including CML harboring the T315I mutation.²¹² Besides its activity against BCR-ABL, ponatinib has also demonstrated inhibition of other tyrosine kinases, including SRC, LYN, and c-KIT as well as members of the vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor families.²¹² Based on these activities, ponatinib has the potential to improve outcomes for patients with CML and/or other malignancies harboring the *BCR-ABL* oncogene (e.g., Ph+ ALL).

Ponatinib is being developed by ARIAD Pharmaceuticals, Inc. (Cambridge, MA). Data from the phase II PACE study of ponatinib for treating patients with TKI-refractory CML or Ph+ ALL demonstrated that treatment with ponatinib resulted in the following:²¹³

- A major cytogenic response rate of 49% for patients with chronic-phase CML
- A major hematologic response rate of 67% for patients with accelerated-phase CML
- A major hematologic response rate of 37% for patients with Ph+ ALL

In June 2012, ARIAD began a phase III, randomized, open-label study of ponatinib versus imatinib in patients with treatment-naïve chronic phase CML (EPIC).²¹⁴ In July 2012, ARIAD submitted an NDA to FDA seeking priority review and accelerated approval of ponatinib for treating resistant or intolerant CML and Ph+ ALL.²¹⁵ In October 2012, FDA accepted ARIAD's NDA filing and request for priority review and established a March 27, 2013, decision date.²¹⁶

Ponatinib is currently available to certain patients in the United States through an expanded access protocol.²¹⁷

Specific pricing information for ponatinib is not available. However, ARIAD has indicated that it will price ponatinib at a 15% to 20% premium to dasatinib and nilotinib, which have an annual wholesale acquisition cost of about \$100,000.²¹⁸

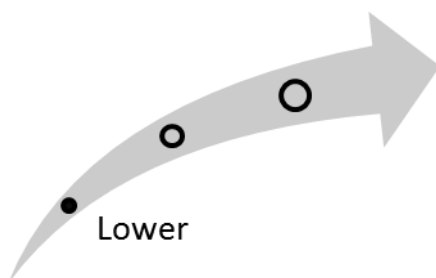
Clinical Pathway at Point of This Intervention

Treatment options for patients in whom CML has been diagnosed depend on the disease phase. Initial treatment of chronic phase CML typically consists of TKI monotherapy with dasatinib, imatinib, or nilotinib. Patients whose disease shows an incomplete response to therapy or relapse during this monotherapy may be switched to a higher dose of the initial inhibitor or switched to a second inhibitor. Treatment of accelerated phase CML often consists of monotherapy with dasatinib or nilotinib, particularly if the patient has not been previously treated with these agents.²¹⁹ Additionally, FDA recently approved omacetaxine mepesuccinate (Synribo[®]) for treating chronic or accelerated-phase CML with resistance or intolerance to two or more TKIs.²²⁰ Some patients in chronic- or accelerated-phase CML may be considered for treatment with hematopoietic stem cell transplant.

Patients in whom CML is initially diagnosed in blast crisis may be treated with TKI therapy followed by hematopoietic stem cell therapy.²¹⁹ Patients whose disease has progressed to blast crisis during TKI therapy are typically treated with regimens usually reserved for acute leukemias (e.g., ALL, acute myeloid leukemia). These treatments typically consist of multiagent chemotherapy regimens that in the case of Ph+ ALL are supplemented with a TKI targeting BCR-ABL.^{221,222} When possible, these chemotherapy regimens are followed by hematopoietic stem cell transplant.^{221,222} Alternatively, patients with Ph+ disease may undergo maintenance therapy using TKIs.^{219,221}

Patients whose disease does not achieve remission or recurs following hematopoietic stem cell transplantation may resume TKI treatment, undergo donor lymphocyte infusion, or undergo interferon treatment.²¹⁹

Figure 9. Overall high-impact potential: multikinase inhibitor (ponatinib) for treatment of chronic myelogenous leukemia or Philadelphia-chromosome-positive acute lymphoblastic leukemia



Overall, experts highlighted the critical role of ponatinib as a therapeutic agent intended for patients with CML or Ph+ ALL that is resistant or intolerant to the currently available TKIs. Several experts noted the importance of data from the ongoing phase III trial in the first-line treatment setting as a determining factor in long-term impact potential. Clinical experts were enthusiastic about the widespread potential for eventual ponatinib use as a monotherapy or as part of combination therapy in first-line treatment settings. However, experts predicted minimal disruption

to existing health care infrastructure and patient management based on the oral administration route and familiar mechanism of action and safety profile. Based on the above, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Eight experts, with clinical, research, and health systems backgrounds, commented on ponatinib.²²³⁻²³⁰

Experts were unanimous about the significant unmet need for patients with CML or Ph+ ALL that is resistant or intolerant to the available TKI therapies, particularly for those with the T315I mutation in *BCR-ABL*. A majority of experts noted the encouraging preliminary data for surrogate endpoints (i.e., major cytogenic response rate, major hematologic response rate), acknowledging significant potential to improve patient health should ongoing trials corroborate initial efficacy data. Several experts also commented on the widespread potential for health benefit with ponatinib use in the first-line setting, possibly in combination with other treatments. Experts with clinical and health systems perspectives believe that ponatinib addresses an important gap in care, and they expected widespread adoption and acceptance by clinicians and patients.

Because ponatinib is an oral medication with a similar or improved safety profile compared with existing TKIs, clinical experts anticipated little disruption to health care infrastructure and patient management as a result its use. One clinical expert noted the potential for increased testing for the T315I mutation that confers resistance to other TKIs.

Given ponatinib's high anticipated drug cost and potential to be used as part of combination therapy during earlier disease phases, experts anticipated slight to moderate cost increases with its use. Among this relatively small patient population, experts suggested, cost could be a deterrent for those without sufficient insurance coverage, but minimal overall effects on health disparities were predicted. Experts noted the potential for cost increases to be offset by postponing or preventing costly treatments such as bone marrow transplantation and by preserving quality of life and the patient's ability to work. A clinical expert also noted that ponatinib may enhance competition with existing TKIs, potentially leading to a decrease in the cost of existing first- and second-line treatments.

It should be noted that omacetaxine mepesuccinate was not yet available at the time of expert comment.

Lung Cancer Intervention

Crizotinib (Xalkori) for Treatment of Advanced Nonsmall Cell Lung Cancer

Patients with advanced nonsmall cell lung cancer (NSCLC) have a relatively low response rate to current therapies (25% to 30%) and result in 2-year survival rates of only 10% to 15%;²³¹ therefore, the need is significant for new treatments for this condition. NSCLC is not a single disease, but rather a collection of related diseases with different molecular underpinnings. In particular, it has been shown that 2% to 7% of NSCLC tumors harbor genetic alterations that result in a fusion of the *ALK* gene with a second gene (e.g., *EML4*). The *ALK* gene encodes a receptor tyrosine kinase that regulates multiple cellular processes, and gene fusions can result in production of an *ALK* protein product that is constitutively active, which can drive carcinogenesis.²³² Targeted inhibition of *ALK* kinase activity is a promising therapeutic alternative for these individuals.

Crizotinib (Xalkori[®], Pfizer, Inc., New York, NY) is an oral chemotherapy drug that functions as an inhibitor of both *ALK* and hepatocyte growth factor receptor tyrosine kinase (MET).²³³ Early clinical trials of crizotinib demonstrated a tumor response in a subset of patients whose tumors harbored an activating *ALK* mutation, and subsequent studies of crizotinib have focused on tumors containing similar *ALK* mutations. A genetic test on a tumor sample is required to identify patients who may benefit from crizotinib therapy.²³²

In a single-arm, phase II study published in 2010, Kwak and colleagues reported on 82 patients with *ALK*-mutation-positive NSCLC who were treated using crizotinib monotherapy.²³² They reported that 57% of patients in the trial had a tumor response based on Response Evaluation Criteria in Solid Tumors criteria (46 partial responses and 1 complete response), and 33% of patients exhibited stable disease after a median treatment duration of 6.4 months. In 2011, FDA approved the drug on the basis of two single-arm trials involving 136 and 119 patients with *ALK*-mutation-positive NSCLC, in whom crizotinib treatment generated an overall objective response rate of 50% and 61%, respectively.²³⁴ The approval was for patients with locally advanced or metastatic NSCLC that is *ALK*-positive as detected by the FDA-approved test, Vysis *ALK* Break Apart FISH Probe Kit.²³⁵ The prescribing information states that the most commonly reported adverse reactions occurring in more than 25% of patients were the following (in decreasing order of all-grades incidence): vision disorder, nausea, diarrhea, vomiting, edema, and constipation.²³⁴ The prescribing information also carries warnings regarding the potential for hepatotoxicity, pneumonitis, and QT interval prolongation.

Two phase III trials of crizotinib in the first- and second-line treatment setting followed up on the phase II trial findings.^{236,237} In September 2012, initial results were presented for the trial of crizotinib in the second-line setting.²³⁸ In this trial, patients with *ALK*-mutation-positive disease who had previously undergone treatment with one platinum drug-containing regimen were randomly assigned to treatment with either crizotinib or cytotoxic chemotherapy (either pemetrexed or docetaxel). Patients in the crizotinib arm demonstrated improved progression-free survival (median 7.7 vs. 3.0 months, HR 0.49; 95% confidence interval, 0.37 to 0.64; $p < 0.0001$); however, overall survival data were immature at the time of presentation.²³⁸

The drug cost is about \$115,000 per patient per year (\$9,600 per month).²³⁹ The list price of the companion diagnostic test is approximately \$225 per test, but the full cost of the test will also include a fee for performing the test.²⁴⁰ Among 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), 9 identified policies indicated that the payer covered crizotinib used in the

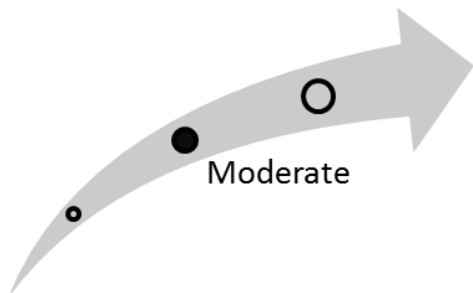
FDA-approved indication of NSCLC.²⁴¹⁻²⁴⁹ Pfizer has a plan that helps reduce patient out-of-pocket costs to \$100 per prescription for copayments for some patients for an annual maximum savings of \$24,000.²³⁹

Pfizer has indicated that adoption of crizotinib for treating patients with *ALK*-mutation-positive NSCLC has been slower than anticipated.²⁵⁰ This may be due, in part, to complications related to testing for presence of the *ALK* mutation in a patient population for whom tumor tissue quantity may be limiting and physicians may want to test for other targetable genetic mutations (e.g., EGFR mutations).²⁵⁰

Clinical Pathway at Point of This Intervention

The initial treatment of NSCLC typically involves surgery to remove the diseased portion of the lung. However, if the tumor is large and/or has spread to adjacent lymph nodes, neoadjuvant chemotherapy and radiation therapy are sometimes used before surgery to reduce the tumor's size. Following surgery, patients may undergo sequential radiation therapy and chemotherapy or combined chemoradiation treatment. Multiple first- and second-line chemotherapy agents are available for treating lung cancer. The choice of one chemotherapy option over the others depends in part on the characteristics of the tumor (e.g., tumor histology, presence of specific genetic changes).²⁵¹ Crizotinib represents another first- or second-line chemotherapy option for patients with cancers bearing a specific genetic change at the *ALK* locus.

Figure 10. Overall high-impact potential: crizotinib (Xalkori) for treatment of advanced nonsmall cell lung cancer



Overall, experts commenting on this intervention thought that it would be readily adopted by physicians and patients and has potential to significantly improve health outcomes for the small (*ALK*-positive) metastatic NSCLC patient population targeted by this drug. Use of the drug requires a test for eligibility, which experts indicated would change the care pathway and add to costs. Its use could also change the care setting because it might supplant infused chemotherapy options with an at-home oral medication. However, experts thought that the limited number of patients who would be eligible for this treatment might limit its overall impact on all patients with NSCLC. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Eight experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.²⁵²⁻²⁵⁹ All experts agreed that a significant unmet need existed for novel therapies for NSCLC, citing the short duration of survival for patients with advanced NSCLC when treated with available therapies. However, several experts noted that the significance of the unmet need purported to be addressed by crizotinib is limited by the fact that the

treatment is targeted to only a small subset of patients with NSCLC that harbors an *ALK* mutation. However, for this select patient population, the majority of experts indicated, the available data suggested that crizotinib has significant potential to improve patient health; the experts cited the high response rate and an indication that crizotinib may improve patient survival. One expert with a clinical perspective suggested that drugs like crizotinib that are intended for a select, targeted patient population with a high rate of response to the therapy should serve as a paradigm for future cancer-drug development. Several experts noted that a clearer picture of the benefits of crizotinib would be generated after the completion of ongoing randomized controlled trials comparing crizotinib with standard treatment options.

The majority of experts did not think that crizotinib would require significant shifts in patient management. Although multiple experts noted that identifying the small number of patients eligible for crizotinib would require screening a large number of patients with NSCLC, some experts noted that this may not represent a major shift, given that molecular testing (e.g., EGFR mutation status) is already routinely performed on biopsy samples from NSCLC patients. Two experts with clinical perspectives suggested that some patients might have to undergo multiple biopsies if insufficient tumor tissue was recovered to perform all necessary molecular diagnostic tests. Besides the additional testing requirements, another reviewer with a clinical perspective suggested that the shift from intravenous chemotherapy agents to an orally administered agent such as crizotinib would require a shift in the way patients are observed for adverse effects of the therapy.

All experts thought that crizotinib would be readily adopted by physicians and patients alike, citing the few viable alternatives, the drug's activity, and the drug's relatively well-tolerated safety profile. Additionally, multiple experts suggested that patients would prefer to take an orally administered medication at home rather than traveling to infusion centers for treatment. However, multiple experts noted the potential for patients to be burdened with a large copayment for crizotinib, which could limit adoption by some patients and could potentially worsen health disparities for certain underserved patient populations.

Prostate Cancer Interventions

Novel Androgen-Targeting Therapies (Abiraterone [Zytiga]; Enzalutamide [Xtandi]) for Metastatic Castration-Resistant Prostate Cancer

Men with metastatic castration-resistant prostate cancer (mCRPC) (i.e., cancer that is insensitive to androgen withdrawal) have few treatment options and a poor prognosis. Recently reported survival time for this patient population when treated using cytotoxic chemotherapy is approximately 22 months.²⁶⁰ Novel treatments for this stage of prostate cancer are highly desired, especially for patients whose disease has progressed after first-line treatment with docetaxel.

mCRPC can progress in presence of castration-level androgens and, therefore, appears to be independent of androgen signaling, which is the primary driver of prostate tumor growth. However, recent research has suggested that these cancers may still depend on androgen receptor signaling; therefore, further inhibition of androgen signaling may have activity as an mCRPC treatment.²⁶⁰

One compound, abiraterone (Zytiga[®], Centocor Ortho Biotech, Inc., which has been acquired by Janssen Biotech, Inc., a unit of Johnson & Johnson, New Brunswick, NJ), is intended to function as an androgen synthesis inhibitor, potentially reducing levels of residual androgens that can drive cancer progression in patients with mCRPC. Abiraterone is an orally administered pregnenolone analog that inhibits the enzyme CYP17, which is involved in a rate-limiting step of androgen biosynthesis.²⁶⁰ A second compound, enzalutamide (Xtandi[®], Medivation, Inc., San Francisco, CA), is intended to inhibit androgen receptor signaling. Enzalutamide is purported to inhibit multiple steps required for androgen receptor activity, including androgen binding, androgen receptor nuclear translocation, and androgen receptor DNA binding.²⁶¹ Unlike currently available androgen receptor antagonists, enzalutamide exhibits no androgen receptor agonist activity.

FDA approved abiraterone in April 2011 for use in combination with prednisone for treating mCRPC that had previously been treated with docetaxel.²⁶² This approval was based on results from a 1,195-patient, phase III, randomized, placebo-controlled trial that showed that overall survival in the abiraterone plus prednisone arm was 15.8 months versus 11.2 months in the placebo plus prednisone arm (HR, 0.74; 95% CI, 0.64 to 0.86; $p < 0.0001$).²⁶³ Researchers reported that common adverse events associated with abiraterone treatment were hypertension, hypokalemia, and edema, which they reported to be manageable through treatment.²⁶⁰ A supplemental NDA for use of abiraterone in chemotherapy-naïve patients was filed in June 2012 based on initial results of a 1,088-patient, phase III, randomized, placebo-controlled trial in this patient population.²⁶⁴ Data reported from an interim analysis of this trial indicated that treatment with abiraterone plus prednisone compared with treatment with placebo plus prednisone lead to a significant increase in progression-free survival and a trend toward an increase in overall survival. At the time of this interim analysis, the trial was unblinded and patients in the control arm were offered treatment with abiraterone.

FDA approved enzalutamide in August 2012 for mCRPC in patients who have previously received treatment with docetaxel.²⁶⁵ This approval was based on results from a phase III, randomized, placebo-controlled trial that showed that overall survival in the enzalutamide arm was 18.4 months versus 13.6 months in the placebo arm (HR 0.63; 95% CI, 0.53 to 0.75; $p < 0.001$).²⁶⁶ Researchers reported that adverse events associated with enzalutamide treatment included fatigue, diarrhea, and hot flashes. Additionally, seizures (a side effect of high-affinity antiandrogens) were reported in 0.6% of patients taking enzalutamide.²⁶⁶ Like abiraterone, enzalutamide is also undergoing study in earlier lines of prostate cancer treatment; a 1,680-patient, phase III trial of enzalutamide for treating patients with chemotherapy-naïve mCRPC completed enrollment in June 2012.²⁶⁷

In the U.S. market, abiraterone has been available since July 2011 and enzalutamide has been available since September 2012. Initial uptake of abiraterone in the postchemotherapy setting has been relatively rapid. In an October 2012 presentation, Johnson & Johnson indicated that in the third quarter of 2012 about two-thirds of patients with prostate cancer being treated in the postdocetaxel setting received treatment with abiraterone.²⁶⁸ Significant off-label use of abiraterone in the prechemotherapy setting has also been reported. Johnson & Johnson estimates that approximately 30% of abiraterone sales are for use in the prechemotherapy setting.²⁶⁹ Release of the preliminary data from the phase III clinical trial of abiraterone in this patient population may spur further adoption.

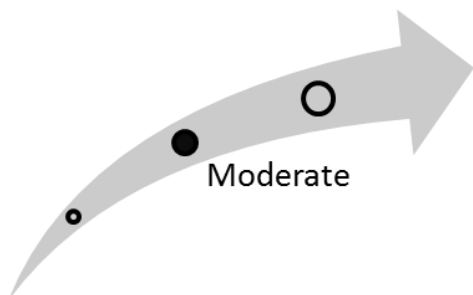
The costs of these new prostate cancer drugs have been reported as \$5,500 and \$7,540 per month of treatment for abiraterone and enzalutamide, respectively.^{270,271} A query of an online pharmacy in November 2012 identified retail prices of \$6,262 and \$8,015 for 1-month supplies of abiraterone and enzalutamide, respectively.^{272,273}

A survey of 11 representative, private, third-party payers that publish their policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) indicated that third-party payers generally reimburse for abiraterone for the FDA-approved indication (i.e., postdocetaxel chemotherapy and in combination with prednisone).²⁷⁴⁻²⁸⁴ The majority of these third-party payers require prior authorization for coverage. Policies regarding enzalutamide are still in the process of being established.

Clinical Pathway at Point of This Intervention

Traditionally, androgen deprivation therapy either by bilateral orchiectomy (surgical castration) or luteinizing hormone-releasing hormone agonist (medical castration) has been used to treat advanced prostate cancer when surgery and/or radiation are not indicated.²⁸⁵ Yet, few options are available for patients whose cancer becomes resistant to androgen deprivation and progresses to mCRPC. mCRPC that is not symptomatic or only mildly symptomatic may be treated with the autologous cancer vaccine sipuleucel-T (Provenge®).²⁸⁵ For patients with more advanced, symptomatic mCRPC, the standard first-line treatment is systemic chemotherapy with the taxane docetaxel.²⁸⁵ Lastly, for patients whose disease progresses after treatment with docetaxel, treatment with the recently approved taxane cabazitaxel in combination with prednisone may be used.²⁸⁵ Abiraterone and enzalutamide represent potential treatment alternatives to cabazitaxel in the postdocetaxel setting and could be used as an alternative to, in sequence with, or in combination with the immunotherapy sipuleucel-T in the predocetaxel/chemotherapy setting.

Figure 11. Overall high-impact potential: novel androgen-targeting therapies (abiraterone [Zytiga]; enzalutamide [Xtandi]) for metastatic castration-resistant prostate cancer



Overall, experts commenting on this intervention were quite positive regarding the potential of abiraterone and enzalutamide to improve both quality and quantity of life for patients with mCRPC.

However, experts pointed out that the demonstrated improvement in survival duration is marginal (a few months) in patients whose disease has not responded to first-line chemotherapy and suggested that these drugs may have a larger impact when used in earlier lines of treatment. Experts suggested that significant study of the proper sequential and/or combinatorial use of abiraterone, enzalutamide, and other recently approved drugs for prostate cancer is needed. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on abiraterone for treating prostate cancer,²⁸⁶⁻²⁹² and nine experts, with clinical research, health systems, and health administration backgrounds, offered perspectives on enzalutamide for treating prostate cancer.²⁹³⁻³⁰¹

Experts uniformly indicated a high unmet need for effective treatments for mCRPC, a need that both abiraterone and enzalutamide purport to address. Experts cited the few treatment options available to these patients and survival rates of short duration using current therapies. In particular, multiple experts suggested a significant need exists for therapies like abiraterone and enzalutamide in treating asymptomatic mCRPC for which currently approved treatments are difficult to administer and/or expensive. Because of the availability of abiraterone, experts commenting on enzalutamide concluded that the unmet need was not large; however, multiple experts suggested that enzalutamide might complement abiraterone or offer an incremental improvement in efficacy and safety compared with abiraterone.

Experts did not believe that abiraterone or enzalutamide would cause a significant shift in health care staffing or health care facility infrastructure requirements because of their nature as orally administered medications. Although use in the postchemotherapy patient population was not seen as leading to a change in patient management, multiple experts suggested that use in earlier stages of disease treatment could shift the care setting for certain patients. All experts suggested that abiraterone and enzalutamide would lead to an increase in the cost of care due to either the addition of a treatment step in the postchemotherapy setting or potential long-term use in earlier stages of treatment.

Although several experts noted that treatment with abiraterone and enzalutamide results in only a modest increase in survival, experts agreed that these drugs would likely be adopted by both patients and physicians because of the promising efficacy results reported in phase III trials, the drugs' ease of use, and their low side-effect profiles relative to chemotherapy.

Radium-223 (Alpharadin) for Treatment of Solid Tumor Bone Metastases

Many cancers, in particular cancers of the breast, prostate, and lung, metastasize to bone, where they can cause complications such as chronic pain and skeletal-related events (e.g., fractures) that can adversely affect both patient quality of life and survival.³⁰² Current treatments targeting bone metastases are largely palliative in nature, providing relief from pain or delaying skeletal-related events without having significant effects on overall disease progression or patient survival. Alpharadin[®] has the potential to be the first bone metastasis-targeted agent that affects both bone metastasis symptoms and patient survival.

Current treatment options for bone metastases include the radionuclides strontium-89 and samarium-153-EDTMP (ethylenediamine tetra [methylene phosphonic acid]), radioactive molecules that have a natural affinity for sites of bone remodeling, which occurs at bone metastases.³⁰² Preferential accumulation of the radioactive compound purportedly concentrates the radiation dose at the target bone metastases. Although available radionuclides have shown efficacy in the palliation of bone pain, the type of radiation that they emit penetrates tissues deeply enough to negatively affect the bone marrow, which limits the deliverable dose and restricts their use to one of symptom palliation.³⁰³ Alpharadin (a preparation of radium-223) is a novel bone metastasis-targeting radiopharmaceutical that emits alpha particles, which have higher energies and more localized activity than the radiation generated by available radiopharmaceuticals.³⁰⁴ This may both reduce the side effects of treatment relative to current radionuclide treatments and improve patient outcomes.³⁰⁴

In June 2012, the developers of Alpharadin (Algeta ASA, Oslo, Norway, and Bayer AG, Leverkusen, Germany) presented results from a randomized, double-blind clinical trial of Alpharadin versus placebo in treating 921 patients with castration-resistant prostate cancer (CRPC) with skeletal metastases who were ineligible for initial treatment or further treatment with docetaxel. In this trial, treatment with Alpharadin was reported to have improved overall survival by 3.6 months versus placebo, representing a 30.5% reduction in the risk of death compared with placebo (two-sided $p=0.00007$). Additionally, Alpharadin treatment prolonged the time to first skeletal-related event by 5.8 months compared with placebo (15.6 vs. 9.8 months; $p=0.00037$; HR=0.658).³⁰⁵

Treatment with Alpharadin was reported as being well tolerated by patients, with the most significant adverse event being myelosuppression. Rates of grade 3 or 4 neutropenia were 2.2% in the Alpharadin arm versus 0.7% in the placebo arm, and rates of grade 3 or 4 thrombocytopenia were 6.3% in the Alpharadin arm versus 2% in the placebo arm.³⁰⁵ Other commonly reported adverse events included bone pain, constipation, diarrhea, nausea, and vomiting; however, rates of the adverse events were similar in the Alpharadin and placebo arms of the trial.³⁰⁶ The relatively benign adverse-event profile of Alpharadin treatment may allow its use in combination with existing cancer treatments. An early-phase, clinical trial is under way testing the combination of Alpharadin with the standard chemotherapy agent docetaxel in treating CRPC.³⁰⁷

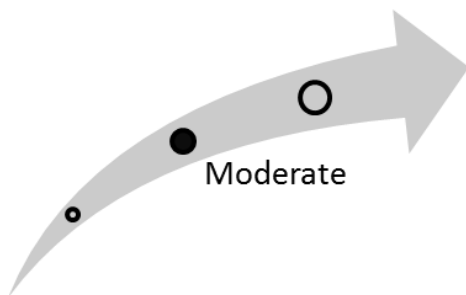
FDA has granted Alpharadin fast-track status for treating CRPC with bone metastases.³⁰⁸ An NDA for this indication was anticipated to be filed some time in 2012; however, no reports of such a submission were identified as of November 2012. Alpharadin is also available as part of an expanded access program for patients with CRPC.^{309,310} An additional agent in development that has shown promise in treating prostate cancer bone metastases is the MET/RET/VEGFR2 kinase

inhibitor cabozantinib; phase III clinical trials of this compound in treating prostate cancer have been initiated.³¹¹

Clinical Pathway at Point of This Intervention

Patients with systemic cancer that has metastasized to bone are typically treated with a combination of locoregional treatment of bone metastases, systemic therapies, and pain medications.³⁰² Palliative local treatments for bone metastases include external beam radiation therapy and surgical resection of the lesion.³¹² Systemic treatments include antineoplastic therapies such as chemotherapy and hormone therapy as well as agents that modulate bone remodeling such as bisphosphonates and the RANKL antibody denosumab.³¹³ Additional systemic agents that are targeted to bone include radiopharmaceuticals such as strontium-89 and samarium-153-EDTMP, which preferentially accumulate in sites of bone metastasis and expose the cancer cells to beta and/or gamma radiation.³⁰² Radium-223 would represent a novel systemic radionuclide treatment for bone metastases that would be the first alpha-particle-emitting radionuclide indicated for treating this condition.

Figure 12. Overall high-impact potential: radium-223 (Alpharadin) for treatment of solid tumor bone metastases



Overall, experts suggested that Alpharadin has significant potential to improve current treatments for bone metastases, particularly for patients with prostate cancer bone metastases. Although experts thought there is significant potential for Alpharadin to be widely adopted for treating bone metastases, the highly similar nature of Alpharadin to existing treatments suggested to experts that adoption of Alpharadin would have limited impact on health care system infrastructure and practices. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.³¹⁴⁻³²⁰ The majority of experts assessed the need for improved treatments for bone metastases as being moderately important or very important, citing the high prevalence of bone metastases in many advanced cancers and the significant impact that these metastases can have on patient quality of life and survival. Experts rating the unmet need addressed by Alpharadin as very important suggested that the compound's purported improved safety profile relative to existing radiopharmaceutical treatments for bone metastases represents a significant improvement. However, one expert with a research perspective who thought the unmet need addressed by Alpharadin was small suggested that the compound represents only an incremental improvement on existing radiopharmaceuticals.

All experts suggested that Alpharadin has moderate to large potential to improve patient health, citing the increased duration of overall survival demonstrated in the recently completed phase III clinical trial and the fact that the toxicity profile for Alpharadin appears to be relatively benign. Additionally, several experts noted the ability of Alpharadin to affect skeletal-related symptoms that affect patient quality of life (e.g., pain) besides its effects on survival and disease progression. One expert with a clinical perspective expressed caution regarding the potential for long-term sequelae of Alpharadin treatment, noting that use of another radium isotope (radium-224) in treating ankylosing spondylitis had led to an increase in leukemia incidence in treated patients. However, the expert also noted that the two radium isotopes have differing decay patterns (which could alter the systemic radiation exposure) and that such long-term sequelae may not be as relevant to patient populations with a poor long-term prognosis (e.g., patients with cancer that has metastasized to bone).

Generally, experts did not think Alpharadin would significantly shift health disparities. A few experts noted that the likely premium price of Alpharadin relative to existing palliative treatments might make the treatment prohibitive for some patients, potentially worsening health disparities. Conversely, one expert with a clinical perspective suggested that underserved populations might present with more advanced disease; therefore, Alpharadin might have a larger impact in these underserved populations.

Experts also did not think that Alpharadin would require significant changes to health care delivery and infrastructure or the manner in which patients are managed, noting the similarity between Alpharadin treatment methods and radiopharmaceuticals now used.

In line with their view that Alpharadin has significant potential to improve health outcomes, the majority of experts suggested that Alpharadin would likely be adopted by physicians and patients alike. Experts cited Alpharadin's reported efficacy in treating prostate cancer bone metastases, ease of use, and routine administration as factors influencing physician adoption and Alpharadin's relatively benign safety profile and potential to improve both severity of bone pain and duration of survival as factors influencing patient adoption. One expert with a research perspective suggested that some patients might be reluctant to opt for a treatment involving infusion of a radioactive isotope; however, this expert still believes that Alpharadin is likely to be widely adopted by patients.

Experts suggested that Alpharadin would likely be priced at a premium relative to current radiotherapy options; therefore, the majority of experts indicated that Alpharadin would increase the overall cost of care. Multiple experts suggested that the potential high cost of this treatment could limit patient adoption if the price is prohibitive for some patients.

Skin Cancer Interventions

Ipilimumab (Yervoy) for Treatment of Metastatic Melanoma

According to the American Academy of Dermatology, more than half of all new cases of melanoma in the United States in 2010 were invasive at the time of diagnosis.³²¹ Until recently, guidelines from the National Comprehensive Cancer Network indicated that no clearly optimal treatments for metastatic melanoma were available, and there was little consensus on standard therapy.³²² The recent approvals of ipilimumab (Yervoy™, Bristol-Myers Squibb, New York, NY) and vemurafenib for treating metastatic melanoma have provided the first treatments that generate any improved survival for this patient population.

Ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking monoclonal antibody intended for treating unresectable or metastatic melanoma. The molecular target of ipilimumab (CTLA-4) is thought to function as a negative regulator of T-cell stimulation. By limiting T-cell activation, CTLA-4 activity may play a role in immune system homeostasis, limiting the magnitude of an immune response and the potential for autoimmune reactions; however, these inhibitory activities may also lead to immune system tolerance of cancer cells. By inhibiting the action of CTLA-4, ipilimumab is believed to increase T-cell activity, resulting in increased antitumor responses generated by the patient's immune system.^{323,324}

In a clinical trial, patients (n=676) with unresectable stage III or IV melanoma whose disease had progressed during therapy were randomly assigned to receive ipilimumab plus the experimental peptide vaccine gp100 (n=403), ipilimumab alone (n=137), or gp100 alone (n=136). Ipilimumab, at a dose of 3 mg/kg of body weight, was administered with or without gp100 every 3 weeks for up to four treatments (induction). The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, compared with 6.4 months among patients receiving gp100 alone (HR for death 0.68; p<0.001). The median overall survival with ipilimumab alone was 10.1 months (HR for death compared with gp100 alone 0.66, p=0.003).³²⁵ In March 2011, FDA granted Bristol-Myers Squibb marketing approval of ipilimumab for treating advanced melanoma.³²⁶ Ipilimumab has a black box warning regarding the development of fatal immune-mediated adverse reactions due to T-cell activation and proliferation, which may involve any organ system; the most common reactions include dermatitis, endocrinopathy, enterocolitis, hepatitis, and neuropathy.³²⁷

Ipilimumab has also been studied in patients with treatment-naïve metastatic melanoma. A 502-patient, phase III clinical trial investigated the efficacy of ipilimumab in combination with the standard first-line chemotherapy agent dacarbazine compared with dacarbazine plus placebo in treating metastatic melanoma. Results published in June 2011 indicated that patients treated with ipilimumab plus dacarbazine exhibited a small but statistically significant improvement in the duration of overall survival compared with dacarbazine alone (11.2 months vs. 9.1 months). Estimated survival rates of the ipilimumab-dacarbazine and dacarbazine-placebo groups were 47.3% and 36.3% at 1 year, 28.5% and 17.9% at 2 years, and 20.8% and 12.2% at 3 years, respectively (HR for death with ipilimumab-dacarbazine 0.72, p<0.001).³²⁸

Although the magnitude of ipilimumab's impact on median overall survival is relatively modest, a subset of patients who receive ipilimumab exhibit durable responses to treatment.^{329,330} Efforts to identify patients likely to have durable responses to ipilimumab have potential to increase the utility of ipilimumab for future patients.

The drug's estimated per-patient cost is \$120,000 for a full course (4 infusions).³³¹ Among 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), policies identified regarding ipilimumab indicated that third-party payers covered the use of ipilimumab for treating

unresectable or metastatic melanoma.³³²⁻³³⁶ The U.S. Centers for Medicare & Medicaid Services has assigned a Healthcare Common Procedure Coding System (HCPCS) code that describes injection of ipilimumab.³³⁷ Bristol-Myers Squibb may provide support to patients unable to afford treatment with ipilimumab through its Yervoy (ipilimumab) patient assistance program.³³⁸

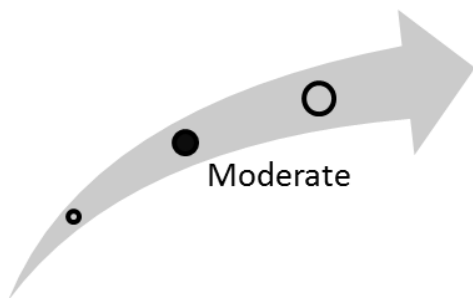
Initial diffusion of ipilimumab has been relatively rapid. A survey of 100 oncologists approximately 1 year after ipilimumab approval indicated that about 25% and 27% of patients with metastatic melanoma are being prescribed ipilimumab in the first- and second-line settings, respectively.³³⁹

Ipilimumab's efficacy has demonstrated the potential of immune checkpoint modulators in melanoma specifically and cancer more generally. Additional therapies targeting immune checkpoints (e.g., programmed cell death protein 1 pathway) are under study in various anticancer indications.³⁴⁰

Clinical Pathway at Point of This Intervention

Patients in whom disseminated/unresectable metastatic melanoma has been diagnosed are typically treated with one of many systemic therapies and/or radiation therapy. Standard systemic therapies include ipilimumab, vemurafenib (for patients whose melanoma harbors an activating mutation in the *B-RAF* gene), dacarbazine, temozolomide, high-dose interleukin-2, or paclitaxel with or without cisplatin or carboplatin. Patients with good enough health to undergo additional treatment may be treated sequentially with additional treatments. Ipilimumab, along with vemurafenib, have become standard first-line options in treating disseminated metastatic melanoma.³⁴¹

Figure 13. Overall high-impact potential: ipilimumab (Yervoy) for treatment of metastatic melanoma



Experts commenting on this intervention thought that clinical trials of ipilimumab demonstrated that the drug has a significant potential to meet an important unmet need for therapies that could improve overall survival in metastatic melanoma. However, this enthusiasm was tempered by the relatively small number of patients who achieve long-term benefit from the drug and the potential for serious adverse events. Despite these caveats, experts believe that ipilimumab would be widely adopted and that the high cost the therapy would have a significant impact on the cost of care for this patient population. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.³⁴²⁻³⁴⁸

Experts unanimously suggested that advanced melanoma represents a very important unmet need, citing the short duration of survival for patients with this condition and the unavailability of

treatments that demonstrated an improvement in overall survival before the recent FDA approval of ipilimumab and the B-RAF inhibitor vemurafenib. The majority of experts believe that the demonstration of improved overall survival in clinical trials involving more than 1,000 patients suggested that ipilimumab has a significant potential to improve the health of patients with metastatic melanoma. In particular, multiple experts with a clinical perspective noted the potential of ipilimumab to generate durable responses, albeit in a small subset of treated patients. Experts who had a less favorable opinion of ipilimumab's potential to improve patient health noted the low overall response rate to ipilimumab therapy and the potential for severe autoimmune-related adverse events.

The majority of experts did not believe that ipilimumab would have a significant impact on health disparities. If anything, experts suggested that the availability of ipilimumab has the potential to exacerbate health disparities. Experts cited the therapy's high cost and the need to travel to an infusion center as potential barriers to the availability of ipilimumab to underserved patient populations.

The majority of experts did not think that ipilimumab would lead to a significant shift in health care facility staffing or infrastructure, given that it would be administered in a manner consistent with other intravenous cancer therapies. However, multiple experts suggested that patient management would need to be altered to allow for monitoring and treatment of emergent autoimmune events associated with ipilimumab treatment. One expert with a clinical perspective suggested that the unpredictable and potentially severe nature of adverse events could limit adoption of ipilimumab therapy to large practice groups and academic centers. However, despite this caveat, the clinical reviewer concurred with the majority of experts who suggested that ipilimumab would be widely adopted by both patients and physicians based on the lack of viable alternative treatments (particularly in patients whose disease does not harbor a *B-RAF* mutation and, therefore, are ineligible for vemurafenib treatment).

Experts agreed that ipilimumab would likely add to the cost of care. Some experts stated that the cost-benefit ratio combined with the potential for life-threatening adverse events may lead to controversy regarding the drug and barriers to its acceptance. One expert with a clinical perspective suggested that the high cost and relatively low response rate would likely lead to studies that attempt to identify patient subgroups that are more likely to respond to ipilimumab therapy. This clinician also suggested that some of the initial enthusiasm for ipilimumab had waned as clinicians and patients looked ahead to other immunotherapies in development.

Vemurafenib (Zelboraf) for Treatment of Metastatic Melanoma

According to the American Academy of Dermatology, more than half of all new cases of melanoma in the United States in 2010 were invasive at the time of diagnosis.³²¹ Until recently, guidelines from the National Comprehensive Cancer Network indicated that no clearly optimal treatments for metastatic melanoma were available, and there was little consensus on standard therapy.³²² The recent approvals of ipilimumab and vemurafenib for treating metastatic melanoma have provided the first treatments that generate a clear improvement in survival for this patient population.

Small-molecule inhibitors of the protein kinase B-RAF represent a recent addition to the metastatic melanoma treatment armamentarium.³⁴¹ B-RAF plays a central role in the RAS/MAP kinase signal transduction pathway, which regulates cell growth and cell proliferation. Misregulation of this pathway has been demonstrated to be involved in multiple cancers, and *B-RAF* gene mutations (e.g., *B-RAF*^{V600E}) encoding a constitutively active B-RAF protein have been identified in about 7% of cancers.³⁴⁹ Although only a small fraction of all human tumors harbor an activating *B-RAF* mutation, more than half of melanomas analyzed have been shown to bear such an allele.³⁴⁹ Activated B-RAF is proposed to lead to hyperactivation of the downstream ERK/MEK/MAP kinase pathway, upon which melanomas may be dependent for growth and survival.³⁵⁰ Therefore, the specific inhibition of B-RAF kinase activity is a promising pharmacologic target. Preclinical studies demonstrated that B-RAF inhibitors were able to inhibit signaling in the downstream MAP kinase pathway only in cells containing the activating *B-RAF*^{V600E} mutation.³⁴⁹ Therefore, most studies have focused on patients whose cancers have been confirmed to contain this mutant form of *B-RAF*.

Vemurafenib (Zelboraf; Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is an orally administered, small-molecule, B-RAF inhibitor. Results were recently reported from the phase III BRIM3 study in which patients with metastatic melanoma (n=675) were randomly assigned to receive either vemurafenib or dacarbazine. In this study, vemurafenib was reported to have met its two primary endpoints of increasing overall survival and increasing progression-free survival relative to treatment with dacarbazine. Researchers reported that treatment with vemurafenib versus dacarbazine was associated with a 63% reduction in the chance of death and a 74% reduction in the chance of either death or disease progression (p<0.001 for both analyses). Commonly reported adverse events associated with vemurafenib treatment included alopecia, arthralgia, diarrhea, fatigue, keratoacanthoma or squamous-cell carcinoma, nausea, photosensitivity, and rash.³⁵¹ A companion diagnostic test (cobas[®] 4800 *B-RAF* V600 Mutation Test) that will allow determination of *B-RAF*^{V600} status was developed in tandem with vemurafenib.³⁵² In August 2011, FDA approved vemurafenib for treating patients with unresectable or metastatic melanoma with the *B-RAF*^{V600E} mutation as detected by an FDA-approved test.^{353,354}

The reported cost of vemurafenib is about \$9,400 per patient per month, and the company estimates a treatment course of about 6 months for a total of about \$56,400 per patient.³⁵⁵ Genentech offers a savings card to reduce out-of-pocket costs for patients with commercial health insurance, and the Genentech Access to Care Foundation may offer assistance to uninsured individuals who cannot afford their prescriptions.^{356,357} Among 11 representative, private, third-party payers that publish their policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), all that had policies covered use of vemurafenib for its FDA-approved indication.^{241,358-361} Additionally, at least two major third-party payers had specific policies that provide coverage for B-RAF^{V600} mutation analysis in individuals with unresectable or metastatic melanoma who are being considered for treatment with vemurafenib.^{362,363}

Initial uptake of vemurafenib has been relatively rapid. Roche estimates that 85% of patients with metastatic melanoma that tests positive for a *B-RAF* mutation receive first-line treatment with vemurafenib.³⁶⁴ *B-RAF* mutation testing has also become relatively routine in patients with metastatic melanoma; physician surveys have indicated that a majority of physicians test at least half their patients for the presence of an activating *B-RAF* mutation.²⁵⁰

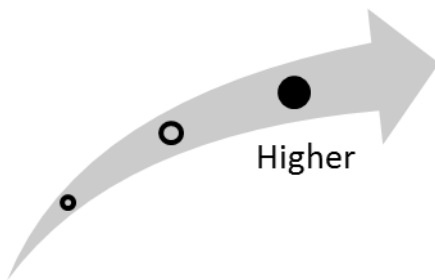
A second B-RAF inhibitor has also reached phase III development: dabrafenib (GlaxoSmithKline, Middlesex, UK). Results of a phase III trial comparing dabrafenib with dacarbazine in treating patients with previously untreated *B-RAF*-mutation-positive, metastatic melanoma were recently reported.³⁶⁵ Median progression-free survival was reported as 5.1 months for patients in the dabrafenib arm compared with 2.7 months for patients in the dacarbazine arm (HR 0.30; 95% CI, 0.18 to 0.51, $p < 0.0001$). On the basis of these results, GlaxoSmithKline submitted an NDA to FDA in August 2012 seeking marketing approval of dabrafenib in treating *B-RAF*-mutation-positive metastatic melanoma.³⁶⁶

One shortcoming of B-RAF inhibitors is the relatively rapid development of resistance to the therapy. To address this issue, researchers are investigating drug combinations that may block certain resistance pathways. Recently, encouraging results were reported for the combination of a B-RAF inhibitor and a MEK inhibitor, and several companies are investigating similar approaches.^{367,368}

Clinical Pathway at Point of This Intervention

Patients in whom disseminated/unresectable, metastatic melanoma has been diagnosed are typically treated with one of several systemic therapies and/or radiation therapy. Standard systemic therapies include dacarbazine, high-dose interleukin-2, ipilimumab, temozolomide, vemurafenib (for patients whose melanoma harbors an activating mutation in the *B-RAF* gene), or paclitaxel with or without cisplatin or carboplatin. Patients maintaining sufficiently good health to undergo additional treatments may be treated sequentially with additional treatments. Vemurafenib and ipilimumab have become standard first-line options in treating disseminated metastatic melanoma.³⁴¹

Figure 14. Overall high-impact potential: vemurafenib (Zelboraf) for treatment of metastatic melanoma



Overall, experts commenting on this drug class believe the availability of B-RAF inhibitors has potential to fundamentally change treatment paradigms for metastatic melanoma because they will split a single syndrome into *B-RAF* mutation-positive and *B-RAF* mutation-negative disease. This will necessitate testing of all patients to determine their *B-RAF* status. Experts opined that although the potential of B-RAF inhibitors is limited because it is unlikely to be a curative treatment and the vast majority of patients will eventually develop resistance to the therapy, these inhibitors are expected to be a central focus of melanoma treatment and clinical study in coming years. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on vemurafenib.³⁶⁹⁻³⁷⁵

Experts were unanimous in their opinion that vemurafenib has potential to address an important unmet need, citing the poor prognosis and limited treatment options for patients with metastatic melanoma and the lack of other therapies targeting oncogenic *B-RAF*. Experts also believe that data from clinical trials indicated that vemurafenib has significant potential to improve patient outcomes, citing a significant increase in the response rate, duration of progression-free survival, and duration of overall survival, but that nearly all patients' disease will eventually become refractory to this treatment and will progress. One expert with a clinical perspective stated that vemurafenib was the only melanoma therapy that frequently generates a rapid tumor response and, therefore, has the potential to provide symptomatic relief to patients.

Experts did not think that the availability of vemurafenib would lead to a marked change in health disparities. One expert with a clinical perspective suggested that an orally administered medication could be more easily administered by local oncologists compared with some other therapies (e.g., high-dose interleukin-2, ipilimumab) that will likely be administered in select centers and so would reach some previously underserved patients. Conversely, an expert with a health administration background suggested that the high cost of vemurafenib and the requirement for *B-RAF* genetic testing could make this treatment prohibitive for underserved patients lacking insurance coverage and/or the economic means to pay for treatment.

As an orally administered medication with a clear target patient population, vemurafenib is not likely to encounter many obstacles to adoption, experts believe. Several experts noted that although vemurafenib has a generally mild side-effect profile, significant side effects have been reported. In particular, the development of squamous cell carcinomas has been associated with *B-RAF* inhibitor treatment and would require that patients be monitored by a dermatologist. However, experts believe that side effects were typically manageable and, given the paucity of treatment options and the potential benefits of the treatment, the potential side effects would not dissuade a significant number of patients or physicians from opting for vemurafenib treatment. Indeed, one expert with a clinical perspective suggested that vemurafenib has already been adopted widely by patients and physicians.

The majority of experts suggested that adding vemurafenib to the clinical pathway for treating *B-RAF*-positive melanoma would lead to a moderate increase in the cost of care for this patient population. Additionally, experts suggested that the need to screen patients with melanoma for *B-RAF* status would add to the cost of treating this condition.

New expert comments have not been received for dabrafenib since the publication of the phase III trial data; therefore, dabrafenib was not considered for inclusion in this iteration of the High-Impact Report. In a previous set of expert comments on dabrafenib, experts suggested that dabrafenib had similar impact potential to vemurafenib, providing that dabrafenib performed well in phase III trials.³⁷⁶⁻³⁸² New expert comments on dabrafenib will be collected for the subsequent High Impact report.

Vismodegib (Erivedge) for Treatment of Advanced Basal Cell Carcinoma

Aberrant activation of the hedgehog signaling pathway drives the development and survival of several tumor types, most prominently basal cell carcinoma, of which the large majority exhibit elevated levels of hedgehog pathway activity.³⁸³ Although pharmacologic inhibition of the pathway would likely be of significant benefit to these patients for whom no consensus systemic treatment exists, no hedgehog pathway inhibitor was available before the recent FDA approval of vismodegib.³⁸⁴

Vismodegib (Genentech subsidiary of Roche) is an orally available, small-molecule antagonist of the hedgehog pathway. Vismodegib functions by inhibiting a protein (called “Smoothed”) that is essential for transducing hedgehog pathway activity. In basal cell carcinomas, mutations may occur that cause constitutive activation of the hedgehog pathway.³⁸⁵ If these mutations affect the pathway at or above the level of Smoothed, vismodegib may be able to reduce the aberrant levels of hedgehog pathway activity and inhibit tumor growth and/or survival.

A recently completed, single-arm, phase II clinical trial (ERIVANCE BCC) studied vismodegib use (150 mg once daily) in 104 patients who had locally advanced and/or metastatic basal cell carcinoma inappropriate for surgical resection. The overall response rate, as assessed by independent review, was 43% ($p=0.001$) in patients with locally advanced disease and 30% ($p=0.001$) in patients with metastatic disease. A complete response was achieved in 21% of patients. Additionally, the median progression-free survival for both patient groups was 9.5 months.³⁸⁶

The most common adverse events reported in the trial included altered taste sensation, decreased appetite, diarrhea, fatigue, hair loss, muscle spasms, nausea, and weight loss. Additionally, serious adverse events were observed in 26 patients (25%) of which 4 (representing 4% of patients) were considered vismodegib-related. These serious adverse events included one case each of blocked bile flow from the liver (cholestasis), dehydration with loss of consciousness (syncope), pneumonia accompanied by an inability of the heart to pump enough blood (cardiac failure), and a sudden arterial blockage in the lung (pulmonary embolism).³⁸⁶

Based on the data from this clinical trial, FDA granted marketing approval for vismodegib in January 2012.³⁸⁴ The prescribing information for vismodegib indicates that the drug is intended for “the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.”³⁸⁷ Ongoing phase II clinical trials are examining the safety and efficacy of vismodegib in patients with operable basal cell carcinoma.^{388,389} Additionally, investigators recently began a phase IIB trial to determine the efficacy of vismodegib for various histologic subtypes of basal cell carcinoma.³⁹⁰ In the future, these data may help clinicians tailor treatment based on the histologic nature of an individual’s basal cell carcinoma.

Genentech announced that vismodegib’s average wholesale cost will be \$7,500 per month per patient, and the estimated duration of treatment is 10 months.³⁹¹ Third-party payers list the drug as a specialty pharmaceutical requiring prior authorization for reimbursement. Genentech’s Access Solutions program facilitates access, including for patients who cannot afford the drug because of large copayments or lack of prescription drug insurance.³⁹² In a mid-year 2012 update, Roche’s partner in developing vismodegib, Curis, Inc. (Lexington, MA), reported a “consistent increase in prescription on a monthly basis over the period since vismodegib launch in February 2012.”³⁹³

Additional evidence for vismodegib’s activity in basal cell carcinoma comes from an investigator-sponsored trial in patients with basal cell nevus syndrome, a genetic condition in which

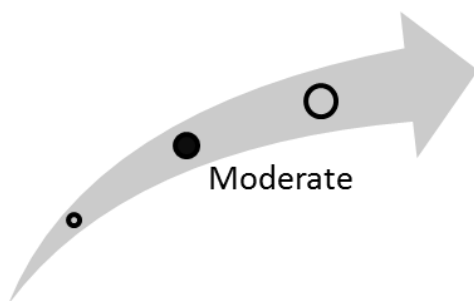
a hereditary defect leads to the formation of large numbers of basal cell carcinomas that each require surgical extirpation. In this 41-patient trial, treatment with vismodegib (150 mg once daily) was compared with treatment with placebo for its ability to prevent the formation of new basal cell carcinomas. An interim analysis indicated that patients treated with vismodegib developed 0.07 new basal cell carcinomas per month compared with 1.74 basal cell carcinomas in patients receiving placebo ($p < 0.0001$). Additionally, vismodegib was reported as leading to a significant reduction in the size of existing basal cell carcinomas.³⁹⁴

Vismodegib and other hedgehog pathway inhibitors are under study in a wide range of cancers, including ovarian and colorectal cancers.^{395,396}

Clinical Pathway at Point of This Intervention

Most basal cell carcinomas are identified as superficial skin lesions and can typically be treated by surgical resection.^{383,397} An alternative primary treatment for these lesions is radiation therapy; however, this treatment is typically reserved for patients older than 60 years of age because of concerns about the potential for collateral tissue damage.³⁹⁷ Lastly, superficial treatments (e.g., photodynamic therapy, cryotherapy, topical chemotherapy) with lower reported cure rates than surgery or radiation therapy might be an option for patients unwilling or unable to undergo surgery or radiation therapy. For basal cell carcinomas that become locally advanced and inoperable or become metastatic, no clear consensus exists on treatment options.³⁹⁷ Treatments include radiation therapy and various systemic chemotherapy options, typically platinum-based cytotoxic regimens.³⁹⁷ Approval of vismodegib provides a new pharmacotherapy option for patients with inoperable/metastatic basal cell carcinomas.^{398,399} Future indications may include the use of vismodegib for operable basal cell carcinomas. Studies are under way to examine the potential benefit as an adjuvant therapy to surgical resection.^{388,389}

Figure 15. Overall high-impact potential: vismodegib (Erivedge) for treatment of advanced basal cell carcinoma



Overall, experts commenting on this intervention believe that vismodegib has significant potential to affect the treatment of basal cell carcinoma as a first-in-class agent that has demonstrated compelling response rates in a patient population lacking a systemic treatment option. However, experts were cautious regarding vismodegib's potential to improve patient health outcomes because of the lack of long-term followup data. Additionally, experts believe that vismodegib's impact on the health system as a whole would be limited by the small target patient population. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁴⁰⁰⁻⁴⁰⁶ Experts thought the unmet need that vismodegib could address is moderately or very important, citing both the lack of effective systemic treatments for advanced/metastatic basal cell carcinoma and the fact that vismodegib represents a first-in-class inhibitor of the hedgehog signaling pathway.

Experts also thought the potential for vismodegib to improve patient health outcomes was moderate to large, citing the relatively high response rates to vismodegib therapy reported in the clinical trial for a patient population with few treatment options. One expert with a clinical perspective observed that vismodegib could be used to downstage large basal cell carcinomas for which surgery would cause significant morbidity and noted that no effective neoadjuvant therapy is available. Experts suggested that vismodegib would be readily adopted by physicians and patients alike, citing the lack of viable treatment alternatives for patients with unresectable basal cell carcinoma. However, two experts suggested that some patients may be hesitant to opt for a therapy with such high rate of side effects, citing the fact that many patients discontinued treatment in the clinical trials of vismodegib. Although experts were enthusiastic regarding the preliminary data on vismodegib's antitumor activity, several experts noted the preliminary nature of these findings, especially with regard to potential long-term side effects of vismodegib treatment.

The majority of experts did not think vismodegib would have a significant impact on health disparities. One expert with a clinical perspective suggested that patients presenting with advanced or unresectable basal cell carcinomas tend to be underserved by the health care system and that vismodegib, which is likely to be an expensive treatment and potentially unavailable to some underserved patients, could worsen this disparity.

Because vismodegib is an orally administered drug that would be taken in the outpatient setting, it would not have significant impacts on health care delivery infrastructure or staffing, the majority of experts thought. However, several experts noted that the way in which patients are managed could be changed in that some patients would be referred to medical oncologists, which would not have occurred, given the lack of systemic therapy options.

Although experts thought that adoption of vismodegib for treating basal cell carcinoma would likely increase the cost of treating these patients, the system-level effect of these costs was seen as minimal because of the relatively small number of patients in whom unresectable basal cell carcinoma is diagnosed each year.

Thyroid Cancer Intervention

Multikinase Inhibitors (Vandetanib [Caprelsa]; Cabozantinib) for Treatment of Metastatic, Medullary Thyroid Cancer

Medullary thyroid cancer is a rare form of thyroid cancer arising from the calcitonin-producing parafollicular (C cells) of the thyroid.⁴⁰⁷ Only about 1,500 cases of medullary thyroid cancer are diagnosed each year in the United States, representing about 3% of thyroid malignancies; however, about 13% of thyroid cancer-related deaths are caused by medullary thyroid cancer, reflecting the paucity of effective treatment options for this condition.^{408,409} In April 2011, FDA approved vandetanib (Caprelsa[®]) as the first and thus far only medication indicated for treating medullary thyroid cancer. Vandetanib is a small-molecule, TKI developed by AstraZeneca (London, UK). The drug has activity against multiple receptor tyrosine kinases, including RET (rearranged during transfection), vascular endothelial growth factor receptor 2 (VEGFR2), and the epidermal growth factor receptor (EGFR).⁴¹⁰ Each of these receptor tyrosine kinases has been shown to regulate pathways controlling cell growth and proliferation, angiogenesis, and survival, and their inhibition has demonstrated antineoplastic activity in treating various cancers.⁴⁰⁹ With regard to medullary thyroid cancer, aberrant RET signaling has been directly implicated in the pathogenesis of the disease; mutant versions of the *RET* gene encoding activated forms of the receptor tyrosine kinase have been identified in both hereditary and sporadic forms of the disease and correlations have been made between the type of *RET* mutation present in an individual and the severity of thyroid tumors occurring in hereditary forms of the disease.^{407,409} Therefore, TKIs with activity against RET (e.g., vandetanib, sorafenib, sunitinib, motesanib, cabozantinib) represent promising treatment options for medullary thyroid cancer.⁴⁰⁹

In October 2011, investigators published results from a double-blind, placebo-controlled study of vandetanib in treating 331 patients who had locally advanced or metastatic medullary thyroid cancer.⁴¹¹ At a median followup of 24 months, patients in the vandetanib arm (n=231) demonstrated a significant improvement in the duration of progression-free survival compared with patients in the placebo arm (n=100; HR, 0.46; 95% CI, 0.31 to 0.69).⁴¹¹ Although researchers attempted to correlate RET mutational status with treatment efficacy, the prescribing information for vandetanib states that no evidence exists of a relationship between RET mutational status and efficacy of treatment.^{407,412} No significant difference in the duration of overall survival had been observed at the time of publication, and while overall survival will continue to be monitored, the result may be obscured by crossover of patients from the placebo arm to treatment with vandetanib.⁴⁰⁷

The prescribing information for vandetanib carries a black box warning regarding the risks of heart rhythm abnormalities (QT prolongation, torsades de pointes) and sudden death.⁴¹² Only prescribers and pharmacies certified through the manufacturer's Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, are allowed to prescribe and dispense vandetanib.⁴¹³ Additional commonly reported adverse events included diarrhea, hypertension, headache, nausea, and rash.⁴¹¹ Because TKIs might be taken over an extended period of time during disease management, adverse events will need to be monitored and managed carefully.

Reported cost of a 30-day supply of 300 mg vandetanib is more than \$10,000. The company created an affordable access program to help patients obtain the drug. Third-party payers list the drug as a specialty pharmaceutical requiring prior authorization.^{241,245,414-421}

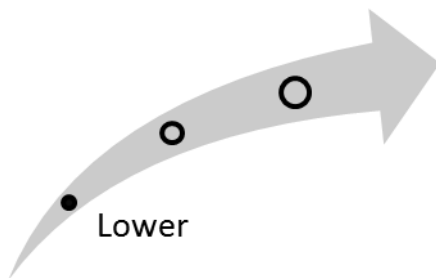
A second TKI, cabozantinib (Exelixis, Inc., South San Francisco, CA), which has activity against RET, VEGFR2, and MET receptor tyrosine kinases has also reached late stages of development.⁴²² In a phase III clinical trial, cabozantinib met its primary endpoint of improving progression-free survival compared with placebo (HR, 0.28; 95% CI, 0.19 to 0.40, p<0.0001) in

patients with medullary thyroid cancer.⁴²³ In this trial, the most frequent adverse events of grade 3 or higher were diarrhea (15.9% cabozantinib arm vs. 1.8% placebo arm), hand-foot syndrome (12.6% cabozantinib vs. 0% placebo), fatigue (9.3% cabozantinib vs. 2.8% placebo), hypocalcemia (9.3% cabozantinib vs. 0% placebo), and hypertension (7.9% cabozantinib vs. 0% placebo).⁴²³ The company completed an NDA with FDA for cabozantinib in treating medullary thyroid cancer in May 2012. FDA has accepted the NDA and granted the submission priority review status with a decision date of November 29, 2012.⁴²⁴

Clinical Pathway at Point of This Intervention

Patients in whom locally advanced, unresectable or metastatic medullary thyroid cancer has been diagnosed have few treatment options. Patients may undergo palliative locoregional treatments such as external beam radiation therapy, radiofrequency ablation, or embolization. Alternatively, patients may undergo treatment with vandetanib, especially in cases of symptomatic or progressive disease. Patients who present with or progress to disseminated symptomatic disease may undergo treatment with vandetanib or, in the case of unavailability of vandetanib or disease progression on vandetanib, other small-molecule, kinase inhibitors (e.g., sorafenib, sunitinib) or dacarbazine-based cytotoxic chemotherapy.⁴²⁵ If approved, cabozantinib would provide another treatment option for patients with advanced disease.

Figure 16. Overall high-impact potential: multikinase inhibitors (vandetanib [Caprelsa]; cabozantinib) for treatment of metastatic, medullary thyroid cancer



Overall, experts commenting on this intervention thought that vandetanib and cabozantinib for treating metastatic medullary thyroid cancer represent a significant improvement in the available treatment options for this patient population, given the prior lack of effective systemic therapy options. However, experts believe that the small population of patients with medullary thyroid cancer eligible for this treatment and the routine nature of its administration would limit the impact of the drugs on the health care system as a whole. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Eight experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of vandetanib for treating medullary thyroid cancer.⁴²⁶⁻⁴³³

From the perspective of the unmet need for systemic treatments for metastatic medullary thyroid cancer, experts agreed that before vandetanib was approved, a significant unmet need existed, citing the lack of efficacious systemic treatments for this condition. However, several experts noted the small number of patients who have medullary thyroid cancer and suggested that a treatment for this condition would have limited impact on the health care system as a whole.

Although one expert with a clinical perspective thought vandetanib's potential to improve patient health was large, other experts viewed the potential as only minimal to moderate. Although all experts pointed to vandetanib's reported effect of increasing the duration of progression-free survival, experts viewing vandetanib's potential more skeptically noted the significant side effects associated with treatment and questioned whether the demonstrated increase in progression-free survival would translate to a significant increase in the duration of overall survival.

Generally, experts did not think that the availability of vandetanib would have a large impact on health disparities. Experts who thought there would be a shift believe that the high cost and limited availability of the drug through the REMS program could worsen health disparities by further limiting access to treatment for underserved patient populations.

Because vandetanib is the first systemic treatment to demonstrate a clear benefit in this patient population, the majority of experts anticipated that both patients and physicians would readily adopt its use in spite of the potential for significant adverse events. However, multiple experts with a research perspective suggested that the adverse-event profile of the drug would limit both clinician and patient adoption to minimal levels. Experts did not think that patient treatment with vandetanib, an orally administered medication, would require significant changes to the health care delivery infrastructure or the manner in which patients are managed. However, multiple experts suggested that the potentially serious adverse events reportedly associated with vandetanib use could increase the required levels of patient management and/or observation compared with other oral oncology drugs.

As a novel medication that would likely be administered over a significant period of time, vandetanib has a moderate to large potential to increase the cost of care for patients with medullary thyroid cancer, the majority of experts thought. However, experts also noted that the small number of patients presenting with metastatic medullary thyroid cancer each year would limit the impact of these costs on the health care system as a whole.

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of cabozantinib for treating medullary thyroid cancer.⁴³⁴⁻⁴³⁹ Expert comments on the potential of cabozantinib for treating medullary thyroid cancer were for the most part similar to those for vandetanib, reflecting the highly similar nature of the two drugs. Although a few experts noted that the availability of vandetanib diminished the unmet need that cabozantinib could fill, one expert with a clinical perspective suggested that both patients and physicians would welcome additional treatment options.

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